IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ABBOTT LABORATORIES and ABBOTT CARDIOVASCULAR SYSTEMS, INC.,	)	
Plaintiffs,	)	
v.	)	C. A. No. 06-613-SLR
JOHNSON AND JOHNSON, INC. and CORDIS CORPORATION,	)	
Defendants.	)	

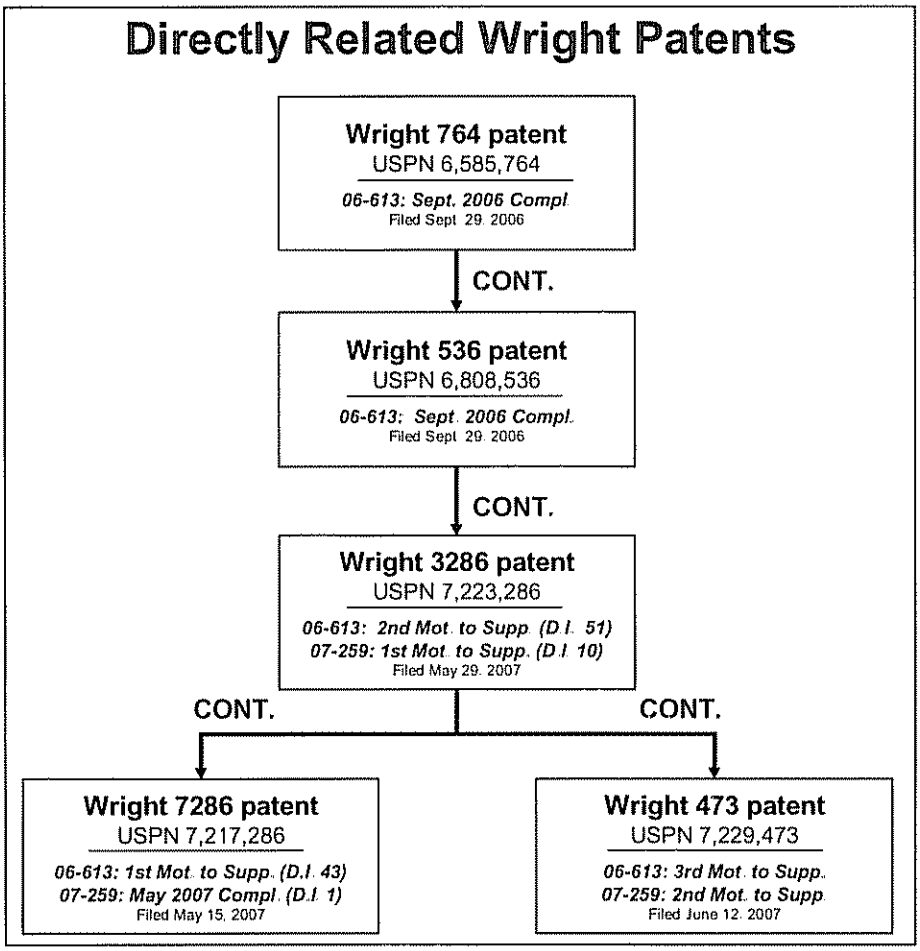
PLAINTIFFS' SECOND SUPPLEMENTAL MOTION FOR LEAVE TO FILE A SUPPLEMENTAL COMPLAINT OR IN THE ALTERNATIVE TO CONSOLIDATE RELATED ACTIONS

Pursuant to Federal Rules of Civil Procedure 15 and 42, Plaintiffs Abbott Laboratories, Inc. and Abbott Cardiovascular Systems, Inc. (collectively, "Abbott") respectfully move for leave to file a supplemental complaint adding a claim for declaratory judgment of invalidity and noninfringement of United States Patent No. 7,229,473 ("the Wright 473 patent"). The present motion is a supplement to two motions to supplement filed by Abbott on May 15, 2007 and May 29, 2007.[1] (*See* D.I. 43 and 51.) Given the interrelatedness of the motions, Defendants have agreed to respond to all of the motions in a single brief to be filed on June 13. (D.I. 55 at 3.) In the alternative, Abbott has requested that the Court consolidate this Civil Action 06-613-SLR with Civil Action No. 07-259-SLR, in which Abbott has also moved to supplement to add the Wright 473

[1] In the May 29 motion to supplement, Abbott advised the Court that the Patent Office would issue U.S. Patent Application No. 11/466,983 (now the Wright 473 patent) on June 12 and that Abbott then would seek to add a declaratory judgment claim relating to that patent. (D.I. 51 at 3, n.2; *id.* at Ex. 4.).) Abbott is doing so now.

patent. Abbott's proposed supplemental Complaint and alternative proposed orders are attached as Exhibit 1 and Attachments A and B, respectively.[2] A redline against the original September 2006 complaint is attached as Exhibit 2.

The Wright 473 patent issued from the Patent Office today. (*See* D.I. 51 at Ex. 4.) As shown in the summary table at right, the Wright 473 patent is directly related to, and has the same specification as, (a) the Wright patents at issue in Plaintiffs' original complaint (U.S. Patent Nos. 6,585,764 and 6,808,536); (b) U.S. Patent No. 7,217,286 (the subject of Abbott's May 15 motion to supplement, D.I. 43); and (c) U.S. Patent No. 7,223,286 (the subject of Abbott's May 29 motion to supplement, D.I. 51). (*See also id.*) Abbott alleges that all five Wright patents are invalid and not infringed by Abbott's XIENCE V drug-eluting stent system. (*See* Ex. 1, Claims I - VI.)



[2] The supplemental Complaint attached as Exhibit 1 includes all the changes proposed in Abbott's May 15 and May 29 motions to supplement and new Claim VI, which is the declaratory judgment claim for the Wright 473 patent.

In summary, whether by supplementation or consolidation, Abbott is seeking to have this Court hear, as a single case, its declaratory judgment claims regarding five directly-related Wright patents and one accused product. For the reasons set forth in Abbott's May 15 and May 29 motions, Abbott respectfully requests that the Court grant Abbott's motions to supplement and allow Abbott to file the Complaint attached as Exhibit 1, which now addresses all five Wright patents.[3] Further, Abbott requests that the supplemental complaint be deemed filed *nunc pro tunc* as of the filing of Abbott's motions to supplement as set forth in the proposed order.

OF COUNSEL:
Edward A. Mas II
Leland G. Hansen
Sandra A. Frantzen
Christopher J. Buchko
McAndrews, Held & Malloy, Ltd.
500 West Madison Street, 34th Floor
Chicago, Illinois 60661
(312) 775-8000

Frederick L. Cottrell III (#2555)
cottrell@RLF.com
Anne Shea Gaza (#4093)
gaza@RLF.com
Richards, Layton & Finger
One Rodney Square
920 N. King Street
Wilmington, Delaware 19899
(302) 651-7700

Attorneys for Plaintiffs
Abbott Laboratories and Abbott
Cardiovascular Systems, Inc.

Date: June 12, 2007

[3] In the alternative, Abbott requests that the Court grant Abbott's motion to consolidate this case with Civil Action No. 07-259-SLR, after granting Abbott's motions to supplement filed in that case. (*See* Attachment B.)

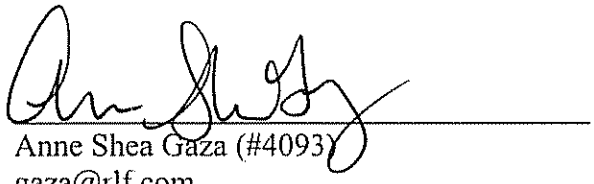
CERTIFICATE OF SERVICE

I hereby certify that on June 12, 2007 I caused to be served by hand delivery the foregoing document and electronically filed the same with the Clerk of Court using CM/ECF which will send notification of such filing(s) to the following:

Steven J. Balick, Esquire
John G. Day, Esquire
Lauren E. Maguire, Esquire
Ashby & Geddes
222 Delaware Avenue, 17th Floor
P.O. Box 1150
Wilmington, DE 19899

I hereby certify that on June 12, 2007, I caused to be sent by Federal Express the foregoing document to the following non-registered participant:

David T. Pritikin, Esquire
William H. Baumgartner, Jr., Esquire
Russell E. Cass, Esquire
Laura L. Kolb, Esquire
Sidley Austin LLP
One South Dearborn
Chicago, IL 60603



Anne Shea Gaza (#4093)
gaza@rlf.com

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ABBOTT LABORATORIES and ABBOTT CARDIOVASCULAR SYSTEMS, INC.,	)	
Plaintiffs,	)	Civil Action No. 06-613-SLR
v.	)	**JURY TRIAL DEMANDED**
JOHNSON AND JOHNSON, INC. and CORDIS CORPORATION,	)	
Defendants.	)	

RULE 7.1.1 CERTIFICATION

Pursuant to District of Delaware Local Rule 7.1.1., undersigned counsel hereby certifies that they have consulted with counsel for defendants regarding the relief sought in Plaintiffs' Supplemental Motion for Leave to File a Supplemental Complaint and were advised that defendants object to the relief sought in the motion.

Frederick L. Cottrell, III (#2555)
cottrell@rlf.com
Anne Shea Gaza (#4093)
gaza@rlf.com
Richards, Layton & Finger, P.A.
One Rodney Square
P.O. Box 551
920 N. King Street
Wilmington, DE 19899
(302) 651-7700
Attorneys for Abbott Laboratories and Abbott Cardiovascular Systems, Inc.

OF COUNSEL:
Edward A. Mas II
Leland G. Hansen
Donald J. Pochopien
Sandra A. Frantzen
Christopher J. Buchko
McAndrews, Held & Malloy, Ltd.
500 West Madison Street, 34th Floor
Chicago, Illinois 60661
(312) 775-8000

Date: June 12, 2007

Exhibit 1

IN THE UNITED STATES DISTRICT COURT FOR THE
DISTRICT OF DELAWARE

ABBOTT LABORATORIES and ABBOTT CARDIOVASCULAR SYSTEMS, INC., Plaintiffs, v. JOHNSON AND JOHNSON, INC. and CORDIS CORPORATION, Defendants.	Civil Action No. 06-613-SLR **JURY TRIAL DEMANDED**

SUPPLEMENTAL AND AMENDED COMPLAINT FOR DECLARATORY JUDGMENT OF PATENT INVALIDITY AND NONINFRINGEMENT

Plaintiffs Abbott Laboratories and Abbott Cardiovascular Systems, Inc. (collectively "Abbott") bring this Supplemental and Amended Complaint against Defendants Johnson and Johnson, Inc. and Cordis Corporation (collectively "J&J"). This is an action for a declaratory judgment and injunctive relief that United States Patent No. 6,585,764 entitled "Stent With Therapeutically Active Dosage Of Rapamycin Coated Thereon" (the "Wright '764 patent"), United States Patent No. 6,808,536 entitled "Stent Containing Rapamycin Or Its Analogs Using A Modified Stent" (the "Wright '536 patent"), United States Patent No. 6,776,796 entitled "Antiinflammatory Drug and Delivery Device" (the "Falotico '796 patent"), United States Patent No. 7,217,286 entitled "Local Delivery of Rapamycin for Treatment of Proliferative Sequelae Associated with PTCA Procedures, Including Delivery Using a Modified Stent" (the "Wright '7286 patent "), United States Patent No. 7,223,286 entitled "Local Delivery Of Rapamycin For Treatment Of Proliferative Sequelae Associated With PTCA Procedures, Including Delivery Using A Modified Stent" (the "Wright '3286 patent"), and United States Patent No. 7,229,473

entitled "Local Delivery of Rapamycin for Treatment of Proliferative Sequelae Associated with PTCA Procedures, Including Delivery Using a Modified Stent" (the "Wright '473 patent") are invalid and not infringed by Abbott. The Wright '764 patent, the Wright '536 patent, the Falotico '796 patent, the Wright '7286 patent, and the Wright '3286 patent are attached as Exhibits A – E, respectively. The Issue Notification for the Wright '473 patent and the Wright '473 patent are attached as Exhibit F. Abbott alleges as follows:

THE PARTIES

1. Abbott Laboratories is a corporation organized under the laws of the State of Illinois and has a principal place of business at 100 Abbott Park Road, North Chicago, Illinois.

2. Abbott Cardiovascular Systems, Inc. ("ACS"), formerly Advanced Cardiovascular Systems, Inc., is a corporation organized under the laws of the State of California and has a principal place of business at 3200 Lakeside Drive, Santa Clara, California. ACS is a subsidiary of Abbott Laboratories.

3. On information and belief, Johnson and Johnson, Inc. is a corporation organized under the laws of the State of New Jersey and has a principal place of business at One Johnson and Johnson Plaza, New Brunswick, New Jersey.

4. On information and belief, Cordis Corporation ("Cordis") is a corporation organized under the laws of the State of Florida and has a principal place of business in Miami Lakes, Florida. Cordis is a subsidiary of Johnson and Johnson, Inc.

JURISDICTION AND VENUE

5. This action arises under the Patent Laws of the United States (35 U.S.C. § 1 *et seq.*).

6. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

7. This Court has personal jurisdiction, general and specific, over J&J.

8. On information and belief, J&J has systematic and continuous contacts in this judicial district.

9. On information and belief, J&J regularly avails itself of the benefits of this judicial district, including the jurisdiction of the courts.

10. On information and belief, J&J regularly transacts business within this judicial district.

11. On information and belief, J&J regularly sells products in this judicial district. J&J derives substantial revenues from sales in this district.

12. Venue is proper in this district under 28 U.S.C. §§ 1391(b) and (c).

BACKGROUND

13. J&J, and in particular Cordis, directly competes with Abbott in the field of intravascular stents used to treat coronary artery disease.

14. The coronary stent industry is highly litigious. J&J, and in particular Cordis, has a well-known history of suing competitors in this field for patent infringement.

15. On three occasions within the last ten years, Cordis sued ACS in this district, alleging patent infringement involving angioplasty catheters or stents for treating coronary artery disease. (*Cordis Corporation, et al. v. Advanced Cardiovascular Systems, Inc, et al.*, C.A. No.

97-550-SLR; *Cordis Corporation, et al. v. Advanced Cardiovascular Systems, Inc., et al.*, C.A. No. 97-635-SLR; and *Cordis Corporation, et al. v. Advanced Cardiovascular Systems, Inc., et al.*, C.A. No. 98-065-SLR).

16. On three additional occasions within the last ten years, Cordis initiated patent infringement actions in this judicial district involving angioplasty catheters or stents for treating coronary artery disease. (*Cordis Corp. v. Boston Scientific Corp.*, C.A. No. 98-197-SLR; *Cordis Corp. v. Medtronic AVE, Inc.*, C.A. No. 00-886-SLR; and *Cordis Corp. v. Boston Scientific Corp.*, C.A. No. 03-027-SLR).

17. In early 2006, J&J and Boston Scientific Corporation ("BSC") each were bidding to acquire assets of Guidant Corporation ("Guidant"), which at the time was the parent corporation of ACS. In conjunction with BSC's bid, ACS would be acquired by Abbott Laboratories, which was the ultimate result.

18. One of the key assets of ACS was the XIENCE V drug eluting stent system ("XIENCE V"), which elutes a proprietary drug known as everolimus. ACS holds an exclusive patent license to use everolimus for drug eluting stents. In clinical trials, everolimus has proven superior to other drugs.

19. On information and belief, J&J believed in early 2006 that the XIENCE V would be launched within a few months.

J&J's Public Threats To Sue For Patent Infringement By XIENCE V

20. On information and belief, J&J undertook a public campaign to cast a cloud over the launch of the XIENCE V.

21. On information and belief, as a main thrust of this public campaign, J&J alleged that the XIENCE V would infringe patents allegedly owned by J&J and that J&J would sue

Abbott for infringement by the XIENCE V following its launch. On information and belief, J&J's allegations related to at least the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

22. On information and belief, J&J broadcasted threatening statements to industry analysts regarding alleged infringement by XIENCE V, for publication in furtherance of J&J's public campaign.

23. For example, the Prudential Equity Group, LLC published a report on January 20, 2006, titled "JNJ: Takes Off The Gloves In Its Fight With Boston Scientific For Guidant," attached as Exhibit G ("the Prudential report"). In the Prudential report, parties are identified by their stock symbols: ABT for Abbott, GDT for Guidant, JNJ for J&J, and BSX for BSC.

24. On information and belief, the Prudential report relied on information provided in pertinent part by J&J.

25. Among other things, the Prudential report stated:

> JNJ claims that 2 of its patents may be infringed if a company tries to launch a drug-eluting stent coated with a rapamycin derivative such as . . . GDT's everolimus. The potential for JNJ to prevent ABT and BSX from marketing the Xience-V DES, could give the GDT board pause for approving a BSX-GDT merger.
>
> * * *
>
> If BSX acquires GDT, BSX would sell GDT's vascular intervention (VI) business, including shared rights to GDT's promising everolimus-coated stent, Xience-V, to ABT. Although JNJ's patents have never been litigated, JNJ believes it has a strong intellectual property (IP) position with regard to the use of

> rapamycin derivatives on a stent. JNJ could pursue a preliminary injunction if ABT and BSX try to launch an everolimus-coated . . . stent. . . . According to JNJ, the key patents are the Falotico (6,776,796) and Wright (6,585,764) patents.

26. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Prudential analysts.

27. On January 23, 2006, A.G. Edwards & Sons, Inc. published a report titled "Healthcare Industry Note: The Game May Be Far From Over," attached as Exhibit H ("the AG Edwards report").

28. On information and belief, the AG Edwards report relied on information provided in pertinent part by J&J.

29. Among other things, the AG Edwards report stated:

> We have had conversations with Johnson & Johnson (JNJ) and Boston Scientific (BSX) and others recently that lead us to believe that the Guidant (GDT) game is far from over.
>
> * * *
>
> We were also reminded by JNJ that it had three patents related to '-limus' compounds that it thought precluded any other company from using such a compound on a stent. We were only given two patent numbers (6776796 [the Falotico '796 patent] and 6585764 [the Wright '764 patent]) . . . .

30. On information and belief, the third patent referenced in J&J's threatening statements was the Wright '536 patent.

31. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to AG Edwards analysts.

32. On January 13, 2006, Citigroup published a report titled "An INTERESTing New Offer," attached as Exhibit I ("the January 13, 2006 Citigroup report").

33. On information and belief, the January 13, 2006 Citigroup report relied on information provided in pertinent part by J&J.

34. Among other things, the January 13, 2006 Citigroup report stated:

> The [Wright and Falotico] patents have never been challenged or enforced because no other company has launched a limus-based drug-eluting stent in the US, but are likely to eventually lead to litigation.

35. Citigroup published an additional report on March 23, 2006 titled "Deconstructing Xience," attached as Exhibit J ("the March 23, 2006 Citigroup report"). In the March 23, 2006 Citigroup report J&J is identified by its stock symbol JNJ.

36. On information and belief, the March 23, 2006 Citigroup report relied on information provided in pertinent part by J&J.

37. Among other things, the March 23, 2006 Citigroup report stated:

> Everolimus will likely face two IP challenges from JNJ as both its Falotico and Wright patents claim the use of a limus analogue on a stent.

38. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Citigroup analysts.

39. On January 30, 2006, Lehman Brothers published a report titled "BSX: The Risks – Part I," attached as Exhibit K ("the Lehman Brothers report"). In the Lehman Brothers report, parties are identified by their stock symbols: ABT for Abbott; GDT for Guidant; and JNJ for J&J.

40. On information and belief, the Lehman Brothers report relied on information provided in pertinent part by J&J.

41. Among other things, the Lehman Brothers report stated:

> There are even hypothetical litigations to contend with as JNJ has strongly suggested that they feel GDT and ABT may violate JNJ/Wyeth DES patents covering the "limus" family of drugs.

42. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Lehman Brothers analysts.

43. On March 14, 2006, Merrill Lynch published a report titled "More legal wrangling for J&J possible," attached as Exhibit L ("the Merrill Lynch report"). In the Merrill Lynch report, J&J is identified by its stock symbol JNJ.

44. On information and belief, the Merrill Lynch report relied on information provided in pertinent part by J&J.

45. Among other things, the Merrill Lynch report stated:

> JNJ has two patents (Wright and Falotico) which appear to relate to the elution of characteristics of "olimus" compounds; JNJ's Cypher DES uses sirolimus, a member of the olimus family of drugs; other olimus drugs include Guidant's everolimus and Abbott/Medtronic's zotarolimus (ABT-578). The European launch of Guidant's Xience DES, which the company has targeted for Q2:06, could trigger possible legal activity since we understand U.S. patent law prohibits domestic manufacture of a product for sale outside the U.S. if there's been infringement of intellectual property.

46. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Merrill Lynch analysts.

47. On information and belief, J&J broadcast threatening statements to other news outlets regarding alleged infringement by XIENCE V, for publication in furtherance of J&J's public campaign.

48. On January 23, 2006, the International Herald Tribune published an article headlined "J&J works to discredit rival offer for Guidant," attached as Exhibit M ("the International Herald article").

49. On information and belief, the International Herald article relied on information provided in pertinent part by J&J.

50. Among other things, the International Herald article stated:

> "J&J is communicating to the Street that Boston Scientific's $80-a-share offer for Guidant is fraught with uncertainty," Lawrence Biegelsen, an analyst with Prudential in New York, said in a note to clients sent on Friday.
>
> * * *
>
> Johnson & Johnson's campaign consists of telling analysts and shareholders that Boston Scientific is in over its head and is tempting patent litigation that may undercut Boston Scientific's plans.
>
> "They're trying to tell all of us that there are patents out there that they have that they feel can stop Boston Scientific," said Jan David Wald, an analyst with A.G. Edwards. Wald said he had been called by a Johnson & Johnson employee, whom he declined to name.

> Johnson & Johnson told analysts it was considering filing patent infringement lawsuits over stent drug coatings to keep Boston Scientific and its bidding partner, Abbott Laboratories, from profiting from the new Guidant devices, according to Biegelsen of Prudential.
>
> * * *
>
> Boston Scientific and J&J have been fighting in court for years over patent-infringement cases related to stent design. At the moment, the two companies are alone in the U.S. stent market, with Boston Scientific holding a 55 percent share.
>
> * * *
>
> The potential for Johnson & Johnson to prevent Abbott and Boston Scientific from marketing Guidant's next-generation heart stent "could give the Guidant board pause for approving a Boston Scientific-Guidant merger," Biegelsen said. "J&J claims that two of its patents may be infringed if a company tries to launch a drug-eluting stent coated with" . . . Guidant's everolimus, he wrote.

51. On January 20, 2006, the Boston Globe published an article headlined "Suitors take Guidant fight to The Street," attached as Exhibit N ("the Boston Globe article").

52. On information and belief, the Boston Globe article relied on information provided in pertinent part by J&J.

53. Among other things, the Boston Globe article stated:

> [J&J] has also raised the prospect that it could use patents and existing ties to Guidant to derail or complicate Boston Scientific's offer, said Matthew Dodds, an analyst for Citigroup who is skeptical about Guidant's value to both companies.

54. Also on January 20, 2006, Crain's Chicago Business published an article headlined "Abbott stock falls on concerns over success of Guidant bid," attached as Exhibit O ("the Crain's article").

55. On information and belief, the Crain's article relied on information provided in pertinent part by J&J.

56. Among other things, the Crain's article stated:

> The analyst, Prudential Equity Group, LLC's Larry Biegelsen, reported that Guidant's board could balk at Boston Scientific and Abbott's joint bid because Johnson & Johnson, a competing bidder for Guidant, claims its patents would be violated if Abbott markets its own drug-eluting stents or those made by Guidant.

57. On January 21, 2006, Reuters published an article headlined "Abbott, Boston shares off on J&J patent threat," attached as Exhibit P ("the Reuters article").

58. On information and belief, the Reuters article relied on information provided in pertinent part by J&J.

59. Among other things, the Reuters article stated:

> One analyst, who asked not to be named, said J&J management was making rounds on Wall Street trying to fan fears about the Boston Scientific bid.
>
> The analyst said J&J was arguing that Boston Scientific's bid was breaking its bank, that its assumptions on Guidant's cardiac rhythm management were too aggressive and that there was intellectual property infringement that would limit potential of important products.

60. On January 24, 2006, Medical Device Daily published an article headlined "J&J offer rumors persist as Guidant has more ICD issues," attached as Exhibit Q ("the Medical Device Daily article").

61. On information and belief, the Medical Device Daily article relied on information provided in pertinent part by J&J.

62. Among other things, the Medical Device Daily article stated:

> Fueling this speculation were rumors, some of which apparently were planted by J&J personnel as part of an organized campaign to undermine the Boston Scientific offer in the minds of analysts, that two of its patents may be infringed if an unnamed company tries to launch a drug-eluting stent coated with a derivative of rapamycin.

63. On January 26, 2006, The Wall Street Journal published an article headlined "Boston Scientific Faces Pivotal Test After Victory in Fight for Guidant," attached as Exhibit R ("the Wall Street Journal article").

64. On information and belief, the Wall Street Journal article relied on information provided in pertinent part by J&J.

65. Among other things, the Wall Street Journal article stated that:

> Another potential wrinkle arises in the intellectual-property rights surrounding stents -- an area that's been the subject of extensive litigation in the industry. Citigroup analyst Matthew Dodds says J&J holds patents on methods of using "limus"-type drugs on stents -- including the everolimus on Guidant's stent, as well as a drug on an Abbott stent.

66. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to analysts and others.

67. On information and belief, J&J made additional threatening statements to industry analysts, asserting that J&J could prevent Abbott from making or selling the XIENCE V by suing for infringement of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent. On information and belief, J&J anticipated and intended that Abbott and others would become aware of these threatening statements.

68. Abbott and others did become aware of J&J's threatening statements.

69. For example, on January 20, 2006, Avram Goldstein of Bloomberg contacted Abbott regarding the Wright and Falotico patents in relation to XIENCE V.

70. On January 13, 2006, Bruce Nudell of Sanford C. Bernstein contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

71. Also on January 13, 2006, The Shaw Group contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

72. On January 20, 2006, Avram Goldstein of Bloomberg contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

73. Again on January 20, 2006, Barnaby Feder of the New York Times contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

74. On January 31, 2006, Steve Silva of Joele Frank contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

75. On March 23, 2006, Jennifer B. Pearlman of Burgundy Asset Management contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

76. On information and belief, in furtherance of its campaign to cast a cloud over the launch of XIENCE V, J&J made threatening statements to Guidant.

77. On January 12, 2006, J&J contacted Guidant and informed Guidant that if Boston Scientific acquired Guidant, Abbott and Boston Scientific would have problems with the Wright and Falotico patent families.

78. On January 13, 2006, J&J again contacted Guidant. J&J sent Guidant a document asserting that J&J's intellectual property portfolio included patents directed to everolimus when used on a stent, Abbott would not receive access to these patents in the event that Boston Scientific were to acquire Guidant, and any drug eluting stent using everolimus, including XIENCE V, may infringe these patents.

79. On information and belief, J&J intended to create a substantial controversy between J&J and Abbott regarding XIENCE V's alleged infringement of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

80. On information and belief, J&J intended to create the apprehension in Abbott and others that J&J would sue Abbott, following the launch of the XIENCE V, asserting that the XIENCE V allegedly infringes the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

81. In March 2006, Guidant publicly announced that the XIENCE V launch would be delayed due to an issue related to manufacturing.

82. As of the date of the original Complaint, the XIENCE V launch was imminent. On information and belief, J&J was aware that the XIENCE V launch was imminent and was preparing to sue Abbott for infringement by the XIENCE V of the Wright '764 patent, the

Wright '536 patent, and the Falotico '796 patent. The XIENCE V subsequently launched in Europe.

83. On information and belief, J&J has never withdrawn or retracted any of its threatening statements that, following the launch of the XIENCE V, J&J would sue Abbott for infringement of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

84. On information and belief, by these statements J&J intended to create a substantial controversy between J&J and Abbott regarding alleged infringement of patents in the Wright and/or Falotico families by XIENCE V.

85. On information and belief, by these statements J&J intended to create the apprehension in Abbott and others that J&J would sue Abbott, following the launch of XIENCE V, asserting that XIENCE V allegedly infringes patents in the Wright and/or Falotico families.

J&J's Assertions In The Patent Office Of Infringement By XIENCE V

86. On August 7, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the First Wright Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 10/951,385 ("Wright '385 application"). The Wright '385 application is related to the Wright '764 patent, the Wright '536 patent, the Wright '7286 patent, and the Wright '473 patent. On May 29, 2007, the Wright '385 application issued as the Wright '3286 patent. A copy of the First Wright Petition is attached as Exhibit S.

87. In the First Wright Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Wright '385 application as a patent. Among other things, counsel for J&J asserted:

Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

* * *

I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of at least claims 103 and 130 on file in this application.

* * *

It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of at least claims 103 and 130 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

88. The subject matter of at least claim 103 of the Wright '385 application overlaps with subject matter claimed in the Wright '764 patent and the Wright '536 patent. Claim 103 of the Wright '385 application issued on May 29, 2007 as claim 40 of the Wright '3286 patent.

89. On information and belief, the subject matter claimed in the Wright '3286 patent is not patentably distinct from subject matter claimed in at least the Wright '7286 patent, the Wright '764 patent, the Wright '536 patent, and/or the Wright '473 patent.

90. On August 24, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the Second Wright Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 11/466,983 ("the Wright '983 application"). The Wright '983 application is related to the Wright '764 patent, the Wright '536

patent, and the Wright '3286 patent. On information and belief, on June 12, 2007, the Wright '983 application issued as the Wright '473 patent. A copy of the Second Wright Petition is attached as Exhibit T.

91. In the Second Wright Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Wright '983 application as a patent. In the Second Wright Petition, J&J's counsel made assertions substantially identical to the assertions made in connection with the First Wright Petition. (*See supra* ¶ 87).

92. The subject matter of at least claim 1 of the Wright '983 application overlaps with subject matter claimed in the Wright '764 patent.

93. On information and belief, the subject matter claimed in the Wright '473 patent is not patentably distinct from subject matter claimed in at least the Wright '7286 patent, the Wright '3286 patent, the Wright '764 patent, and/or the Wright '536 patent.

94. On August 24, 2006, J&J filed another "Petition to Make Special Because of Actual Infringement" ("the Third Wright Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 11/467,035 ("the Wright '035 application"). The Wright '035 application is related to the Wright '764 patent, the Wright '536 patent, and the Wright '3286 patent. On May 15, 2007, the Wright '035 application issued as the Wright '7286 patent. A copy of the Third Wright Petition is attached as Exhibit U.

95. In the Third Wright Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Wright '035 application as a patent. In the Third Wright Petition, J&J's counsel made assertions substantially identical to the assertions made in connection with the First Wright Petition. (*See supra* ¶ 87).

96. The subject matter of at least claim 1 of the Wright '7286 patent overlaps with subject matter claimed in the Wright '764 patent.

97. The subject matter claimed in the Wright '7286 patent is not patentably distinct from subject matter claimed in at least the Wright '3286 patent, the Wright '473 patent, the Wright '764 patent, and/or the Wright '536 patent.

98. On information and belief, J&J is preparing to assert, and has asserted, one or more patents in the Wright family, including at least the Wright '764 patent, the Wright '536 patent, the Wright '7286 patent, the Wright '3286 patent, and the Wright '473 patent against the XIENCE V.

99. On August 7, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the First Falotico Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 10/829,074 ("the Falotico '074 application"). The Falotico '074 application is related to the Falotico '796 patent. A copy of the First Falotico Petition is attached as Exhibit V.

100. In the First Falotico Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Falotico '074 application as a patent. Among other things, counsel for J&J asserted:

> Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).
>
> * * *
>
> I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases and other publicly available documents, with the claims of

the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of claims 15 to 30 on file in this application.

* * *

It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of claims 15 to 30 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

101. The subject matter of at least claim 15 of the Falotico '074 application overlaps with subject matter claimed in the Falotico '796 patent.

102. On August 7, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the Second Falotico Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 10/852,517 ("the Falotico '517 application"). The Falotico '517 application is related to the Falotico '796 patent. A copy of the Second Falotico Petition is attached as Exhibit W.

103. In the Second Falotico Petition, J&J asserted that it could sue Abbott for infringement by XIENCE V immediately upon issuance of the Falotico '517 application as a patent. In the Second Falotico Petition, J&J's counsel made assertions substantially identical to the assertions made in connection with the First Falotico Petition. (*See supra* ¶ 100).

104. The subject matter of at least claim 5 of the Falotico '517 application overlaps with subject matter claimed in the Falotico '796 patent.

105. On August 24, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the Third Falotico Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 11/467,099 ("the Falotico '099

application"). The Falotico '099 application is related to the Falotico '796 patent. A copy of the Third Falotico Petition is attached as Exhibit X.

106. In the Third Falotico Petition, J&J asserted that it could sue Abbott for infringement by XIENCE V immediately upon issuance of the Falotico '099 application as a patent. In the Third Falotico Petition, J&J's counsel made assertions substantially identical to the assertions made in connection with the First Falotico Petition. (*See supra* ¶ 100).

107. The subject matter of at least claim 1 of the Falotico '099 application overlaps with subject matter claimed in the Falotico '796 patent.

108. On information and belief, J&J is preparing to assert one or more patents in the Falotico family, including at least the Falotico '796 patent, against the XIENCE V.

J&J Has Recently Sued Abbott In An Attempt To Interfere With The XIENCE V Launch

109. On September 25, 2006, J&J filed a complaint in the District Court for the Southern District of New York. Among other things, J&J alleges that Abbott Laboratories tortiously interfered with J&J's intended acquisition of Guidant. The complaint seeks no less than $5.5 billion in damages. A copy of the complaint is attached as Exhibit Y.

110. Although the events cited in the complaint occurred over eight months ago, J&J timed the lawsuit, on information and belief, in anticipation of the then imminent launch of XIENCE V. Both the timing of the lawsuit and the amount of the damages claimed manifest J&J's intent to cast a cloud over Abbott and interfere with the then imminent launch of the XIENCE V.

The XIENCE V Launch

111. As of the date of the original Complaint, Abbott had manufactured, at its facilities in the United States, thousands of XIENCE V products to support its launch.

112. Abbott has continued to manufacture XIENCE V at its facilities in the United States following the launch.

113. J&J created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Wright '764 patent, the Wright '536 patent, the Falotico '796 patent, the Wright '7286 patent, the Wright '3286 patent, and the Wright '473 patent by XIENCE V.

114. Abbott has a reasonable apprehension that J&J intends to sue Abbott for infringement of the Wright '764 patent, the Wright '536 patent, the Falotico '796 patent, the Wright '7286 patent, the Wright '3286 patent, and the Wright '473 patent by XIENCE V.

CLAIM I

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 6,585,764

115. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-114.

116. J&J's actions have created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Wright '764 patent by XIENCE V.

117. J&J has asserted rights under the Wright '764 patent against the XIENCE V.

118. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '764 patent by XIENCE V.

119. On information and belief, the claims of the Wright '764 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

120. The XIENCE V does not infringe any valid claim of the Wright '764 patent.

121. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '764 patent.

CLAIM II

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 6,808,536

122. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-121.

123. J&J's actions have created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Wright '536 patent by XIENCE V.

124. J&J has asserted rights under the Wright '536 patent against the XIENCE V.

125. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '536 patent by XIENCE V.

126. On information and belief, the claims of the Wright '536 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

127. The XIENCE V does not infringe any valid claim of the Wright '536 patent.

128. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '536 patent.

CLAIM III

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 6,776,796

129. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-128.

130. J&J's actions have created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Falotico '796 patent by XIENCE V.

131. J&J has asserted rights under the Falotico '796 patent against the XIENCE V.

132. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Falotico '796 patent by XIENCE V.

133. On information and belief, the claims of the Falotico '796 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

134. The XIENCE V does not infringe any valid claim of the Falotico '796 patent.

135. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Falotico '796 patent.

CLAIM IV

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 7,217,286

136. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-135.

137. The Wright '7286 patent issued on May 15, 2007.

138. J&J's actions have created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Wright '7286 patent by XIENCE V.

139. J&J has asserted rights under the Wright '7286 patent against the XIENCE V.

140. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '7286 patent by XIENCE V.

141. On information and belief, the claims of the Wright '7286 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

142. The XIENCE V does not infringe any valid claim of the Wright '7286 patent.

143. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '7286 patent.

CLAIM V

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 7,223,286

144. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-143.

145. The Wright '3286 patent issued on May 29, 2007.

146. J&J's actions have created a substantial controversy between J&J and Abbott regarding alleged infringement of the Wright '3286 patent by XIENCE V.

147. J&J has asserted rights under the Wright '3286 patent against the XIENCE V.

148. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '3286 patent by XIENCE V.

149. On information and belief, the claims of the Wright '3286 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

150. The XIENCE V does not infringe any valid claim of the Wright '3286 patent.

151. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '3286 patent.

CLAIM VI

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 7,229,473

152. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-151.

153. On information and belief, the Wright '473 patent issued on June 12, 2007.

154. J&J's actions have created a substantial controversy between J&J and Abbott regarding alleged infringement of the Wright '473 patent by XIENCE V.

155. J&J has asserted rights under the Wright '473 patent against the XIENCE V.

156. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '473 patent by XIENCE V.

157. On information and belief, the claims of the Wright '473 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

158. The XIENCE V does not infringe any valid claim of the Wright '473 patent.

159. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '473 patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request entry of judgment in their favor that:

(a) each and every claim of U.S. Patent No. 6,585,764 is invalid;

(b) each and every claim of U.S. Patent No. 6,808,536 is invalid;

(c) each and every claim of U.S. Patent No. 6,776,796 is invalid;

(d) each and every claim of U.S. Patent No. 7,217,286 is invalid;

(e) each and every claim of U.S. Patent No. 7,223,286 is invalid;

(f) each and every claim of U.S. Patent No. 7,229,473 is invalid;

(g) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 6,585,764;

(h) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 6,808,536;

(i) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 6,776,796;

(j) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 7,217,286;

(k) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 7,223,286;

(l) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 7,229,473;

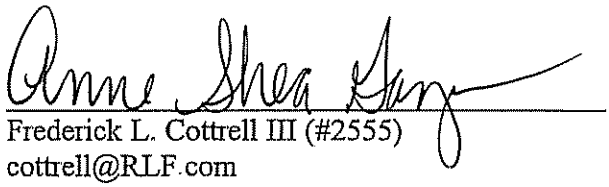
(m) Defendants and their officers, agents, employees, representatives, counsel and all persons in active concert or participation with any of them, directly or indirectly, be enjoined from threatening or charging infringement of, or instituting any action for infringement of any of U.S. Patent Nos. 6,585,764, 6,808,536, 6,776,796, 7,217,286, 7,223,286, and 7,229,473 against Plaintiffs, their suppliers, customers, distributors or users of their products;

(n) Defendants pay to Plaintiffs the costs and reasonable attorneys fees incurred by Plaintiffs in this action; and

(o) Plaintiffs be granted such other and further relief as this Court deems just and proper.

JURY TRIAL DEMANDED

Plaintiffs demand a trial by jury on all issues so triable.



Frederick L. Cottrell III (#2555)
cottrell@RLF.com
Anne Shea Gaza (#4093)
gaza@RLF.com
RICHARDS, LAYTON & FINGER
One Rodney Square
920 N. King Street

OF COUNSEL:
Edward A. Mas II
Leland G. Hansen
Sandra A. Frantzen
Christopher J. Buchko
MCANDREWS, HELD & MALLOY, LTD.
500 West Madison Street, 34th Floor

Chicago, Illinois 60661
(312) 775-8000

Wilmington, Delaware 19899
(302) 651-7700

ATTORNEYS FOR PLAINTIFFS ABBOTT LABORATORIES and ABBOTT CARDIOVASCULAR SYSTEMS, INC.

Date: June 12, 2007

Exhibit A

US006585764B2

(12) **United States Patent**
Wright et al.

(10) **Patent No.: US 6,585,764 B2**
(45) **Date of Patent: Jul. 1, 2003**

(54) **STENT WITH THERAPEUTICALLY ACTIVE DOSAGE OF RAPAMYCIN COATED THEREON**

(75) Inventors: **Carol Wright**, Somerset, NJ (US); **Gerard H. Llanos**, Stewartsville, NJ (US); **Ronald Rakos**, Middlesex County, NJ (US); **Kristen King**, Hoboken, NJ (US)

(73) Assignee: **Cordis Corporation**, Miami Lakes, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/874,117**

(22) Filed: **Jun. 4, 2001**

(65) **Prior Publication Data**

US 2001/0027340 A1 Oct. 4, 2001

Related U.S. Application Data

(63) Continuation of application No. 09/061,568, filed on Apr. 16, 1998, now Pat. No. 6,273,913.
(60) Provisional application No. 60/044,692, filed on Apr. 18, 1997.

(51) **Int. Cl.**[7] **A61F 2/06**

(52) **U.S. Cl.** **623/1.42**

(58) **Field of Search** 623/1.15, 1.39, 623/1.42, 1.4; 427/2.1–2.31

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,234,456	A	8/1993	Silvestini
5,282,823	A	2/1994	Schwartz et al.
5,283,257	A	2/1994	Gregory et al.
5,288,711	A	2/1994	Mitchell et al.
5,342,348	A	8/1994	Kaplan
5,383,928	A	1/1995	Scott et al.
5,443,496	A	8/1995	Schwartz et al.
5,449,382	A	9/1995	Dayton
5,464,450	A	11/1995	Buscemi et al.
5,464,650	A	11/1995	Berg et al.
5,500,013	A	3/1996	Buscemi et al.
5,510,077	A	4/1996	Dinh et al.

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

EP	0 712 615	5/1996
EP	0 716 836	6/1996
EP	0 761 251	3/1997
EP	0 850 651	7/1998
EP	0 938 878 A3	9/1999
EP	0 938 878 A2	9/1999
WO	WO96/32907	10/1996
WO	WO97/33534 A1	9/1997
WO	WO98/23228	6/1998
WO	WO98/34669	8/1998
WO	WO98/47447 A1	10/1998
WO	WO98/56312	12/1998

OTHER PUBLICATIONS

Marx, Steven O. et al., Rapamycin–FKBP Inhibits Cell Cycle Regulators of Proliferation in Vascular Smooth Muscle Cells, Circulation Research, 1995;76(3):412–417.

Serruys, Patrick W. et al., Heparin–Coated Palmaz–Schatz Stents in Human Coronary Arteries, Circulation. 1996;93;412–422.

Lundergan, Conor F., MD et al., Peptide Inhibition of Myointimal Proliferation by Angiopeptin, a Somatostatin Analogue, JACC vol. 17, No. 6, May 1991:132B–6B.

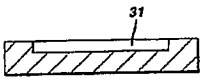
(List continued on next page.)

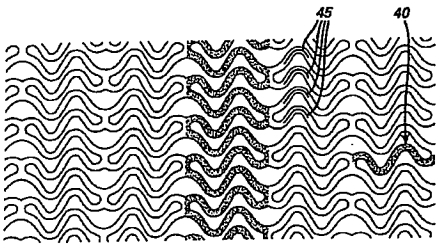
Primary Examiner—David H. Willse
Assistant Examiner—Suzette J. Jackson
(74) *Attorney, Agent, or Firm*—Paul A. Coletti

(57) **ABSTRACT**

Delivery of rapamycin locally, particularly from intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

20 Claims, 2 Drawing Sheets





U.S. PATENT DOCUMENTS

5,516,781 A		5/1996	Morris et al.	
5,545,208 A		8/1996	Wolff et al.	
5,551,954 A		9/1996	Buscemi et al.	
5,554,182 A		9/1996	Dinh et al.	
5,562,922 A		10/1996	Lambert	
5,563,146 A		10/1996	Morris et al.	
5,571,166 A		11/1996	Dinh et al.	
5,578,075 A		11/1996	Dayton	
5,591,224 A		1/1997	Schwartz et al.	
5,591,227 A		1/1997	Dinh et al.	
5,599,352 A		2/1997	Dinh et al.	
5,603,722 A		2/1997	Phan et al.	
5,605,696 A		2/1997	Eury et al.	
5,607,463 A		3/1997	Schwartz et al.	
5,607,475 A		3/1997	Cahalan et al.	
5,609,629 A		3/1997	Feamot et al.	
5,624,411 A		4/1997	Tuch	
5,628,785 A		5/1997	Schwartz et al.	
5,629,077 A		5/1997	Turnlund et al.	
5,632,840 A		5/1997	Campbell	
5,637,113 A		6/1997	Tartaglia et al.	
5,646,160 A		7/1997	Morris et al.	
5,649,977 A		7/1997	Campbell	
5,651,174 A		7/1997	Schwartz et al.	
5,665,591 A	*	9/1997	Sonenshein et al.	435/375
5,672,638 A		9/1997	Verhoeven et al.	
5,674,242 A		10/1997	Phan et al.	
5,679,400 A		10/1997	Tuch	
5,679,659 A		10/1997	Verhoeven et al.	
5,693,085 A		12/1997	Buirge et al.	
5,697,967 A		12/1997	Dinh et al.	
5,700,286 A		12/1997	Tartaglia et al.	
5,707,385 A		1/1998	Williams	
5,725,567 A		3/1998	Wolff et al.	
5,728,150 A		3/1998	McDonald et al.	
5,728,420 A		3/1998	Keogh	
5,733,327 A		3/1998	Igaki et al.	
5,735,897 A		4/1998	Buirge	
5,755,772 A		5/1998	Evans et al.	
5,769,883 A		6/1998	Buscemi et al.	
5,776,184 A		7/1998	Tuch	
5,782,908 A		7/1998	Cahalan et al.	
5,788,979 A		8/1998	Alt et al.	
5,799,384 A		9/1998	Schwartz et al.	
5,800,507 A		9/1998	Schwartz	
5,820,917 A		10/1998	Tuch	
5,820,918 A		10/1998	Ronan et al.	
5,824,048 A		10/1998	Tuch	
5,824,049 A		10/1998	Ragheb et al.	
5,833,651 A		11/1998	Donovan et al.	
5,837,008 A		11/1998	Berg et al.	
5,837,313 A		11/1998	Ding et al.	
5,843,172 A		12/1998	Yan	
5,849,034 A		12/1998	Schwartz	
5,851,217 A		12/1998	Wolff et al.	
5,851,231 A		12/1998	Wolff et al.	
5,865,814 A		2/1999	Tuch	
5,871,535 A		2/1999	Wolff et al.	
5,879,697 A		3/1999	Ding et al.	
5,882,335 A		3/1999	Leone et al.	
5,893,840 A	*	4/1999	Hull et al.	604/96
5,932,243 A	*	8/1999	Fricker et al.	424/450
5,968,091 A	*	10/1999	Pinchuk et al.	623/1.15
6,015,432 A	*	1/2000	Rakos et al.	623/1.15
6,153,252 A	*	11/2000	Hossainy et al.	427/2.3
6,273,913 B1	*	8/2001	Wright et al.	623/1.42
6,369,039 B1	*	4/2002	Palasis et al.	514/44

OTHER PUBLICATIONS

Liu, Ming Wei, MD et al., Restenosis After Coronary Angioplasty Potential Biologic Determinants and Role of Intimal Hyperplasia, Circulation 1989, 79;1374–1387.

Serruys, P. W. et al., Evaluation of Ketanserin in the Prevention of Restenosis After Percutaneous Transluminal Coronary Angioplasty –A Multicenter Randomized Double–Blind Placebo–Controlled Trial, Circulation vol. 88, No. 4, Part 1, Oct. 1993; 1588–1601.

Berk, Bradford C. MD et al., Pharmacologic Roles of Heparin and Glucocorticoids to Prevent Restenosis After Coronary Angioplasty, JACC vol. 17, No. 6, May 1991;111B–7B.

Serruys, Patrick W. MD et al. A Comparison of Balloon–xpandable–Stent Implantation with Balloon Angioplasty in Patients with Coronary Artery Disease. The New England Journal of Medicine, vol. 331, No. 8, Aug. 25, 1994, 489–495.

Fischman, David L. MD et al., A Randomized Comparison of Coronary–Stent Placement and Balloon Angioplasty in Patients with Coronary Artery Disease. The New England Journal of Medicine, vol. 331, No. 8, Aug. 25, 1994, 496–501.

Colburn Michael D. MD et al., Dose Responsive suppression of myointimal hyperlesia by dexemethasone, Journal of Vascular Surgery, vol. 15, No. 3, Mar. 1992, 510–518.

Liu Ming, W. MD, Trapidil in Preventing Restenosis After Balloon Angioplasty in the Atherosclerotic Rabbit, Circulation, vol. 81, No. 3, Mar. 1990, 1089–1093.

Hansson, Goran K. MD, et al., Interferon–Inhibits Arterial Stenosis After Injury, Circulation, vol. 84, No. 3, Sep. 1991, 1266–1272.

Snow, Alan D. et al., Heparin Modulates the Composition of th Extracellular Matrix Domain Surrounding Arterial Smooth Muscle Cells, American Journal of Pathology, vol. 137, No. 2, Aug. 1990, 313–330.

Popma, Jeffrey J. MD et al., Clinical Trials of Restenosis After Coronary Angioplasty, Circulation vol. 84, No. 3, Sep. 1991, 1426–1436.

Campbell, Gordon R. et al., Phenotypic Modulation of Smooth Muscle Cells in Primary Culture, Vascular Smooth Muscle Cells in Culture, CRC Press 1987, pp. 39–55.

Clowes, Alexander W. et al., Significance of Quiescent Smooth Muscle Migration in the Injured Rat Carotid Artery. Cir Res 58: 139–145 1985.

Lange, Richard A. MD et al., Restenosis After Coronary Balloon Angioplasty, Annu. Rev. Med. 1991, 42:127–132.

Franklin, Stephen, M. MD et al., Pharmacologic prevention of restenosis after coronary angioplasty: review of the randomized clinical trials, Coronary Artery Disease, Mar. 1993, vol. 4, No. 3, 232–242.

Suppression by heparin of smooth cell proliferation in injured arteries. Nature, vol. 265, Feb. 17, 1977, 625–626.

Guyton, John, R. et al., Inhibition of Rat Arterial Smooth Muscle Cell Proliferation by Heparin. Circulation Research, vol. 48, No. 5, May 1980, 625–634.

Clowes, Alexander W. et al., Kinetics of Cellular Proliferation after Arterial Injury, Circulation Reseach, vol. 58, No. 6, Jun. 1988, 839–845.

Majesky, Mark W., et al., Heparin Regulates Smooth Muscle S Phase Entry in the Injured Rat Carotid Artery. Circulation Research, vol. 61, No. 2, Aug. 1987, 296–300.

Okada, Tomohisa, MD et al., Localized Release of Perivascular Heparin Inhibits Intimal Proliferation after Endothelial Injury without Systemic Anticoagulation, Neurosurgery, vol. 25, No. 6, 1989, 892–898.

Vasey, Charles G. et al., Clinical Cardiology, Stress Echo and Coronary Flow, Supplement II Circulation, vol. 80, No. 4, Oct. 1989, II–66.

Powell, Jerry S., et al., Inhibitors of Angiotensin–Converting Enzyme Prevent Myointimal Proliferation After Vascular Injury, Science, vol. 245, Jul. 14, 1989, 186–188.

Jonasson, Lena et al., Cyclosporin A Inhibits smooth muscle proliferation in the vascular response to injury. Proc. Natl. Acad. Sci USA 85 (1988), pp. 2303–2308.

Nemecek, Georgina M. et al., Terbinafine Inhibits the Mitogenic Response to Platelet–Derived Growth Factor in Vitro and Neointimal Proliferation in Vivo. The Journal of Pharmacology and Experimental Therapeutics, vol. 248, No. 3, 1998, 1167–1174.

Siekierka, John J., Probing T–Cell Signal Transduction Pathways with the Immunosuppressive Drugs, FK–506 and Rapamycin, Immunologic Research 1994, 13:110–116.

Poon, Michael et al., Rapamycin Inhibits Vascular Smooth Muscle Cell Migration. J. Clin. Invest., vol. 98, No. 10, Nov. 1996, 2277–2283.

Gregory, Clare R. et al., Rapamycin Inhibits Arterial Intimal Thickening Caused by Both AlloImmune and Mechanical Injury, Transplantation vol. 55, No. 6, Jun. 1993, 1409–1418.

* cited by examiner

FIG. 1

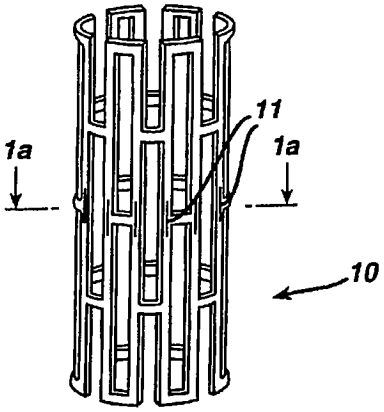


FIG. 1a

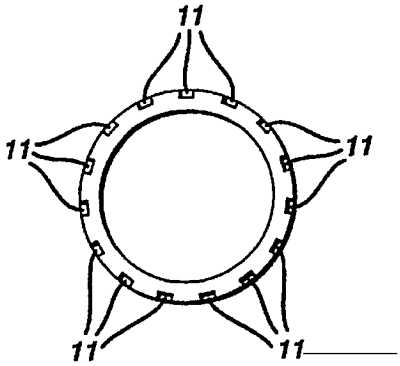


FIG. 2a

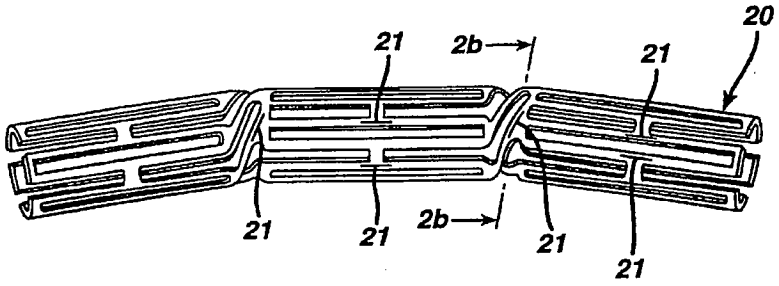


FIG. 2b

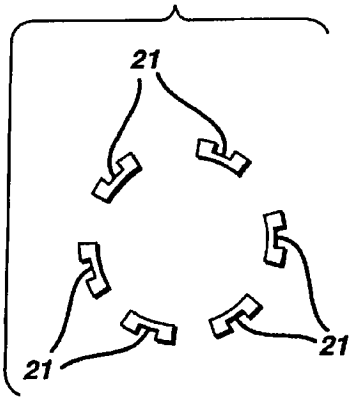


FIG. 3a

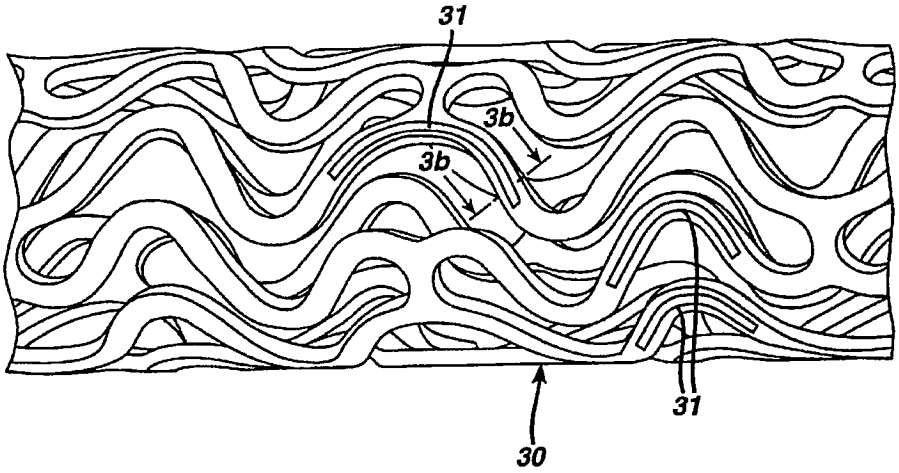


FIG. 3b

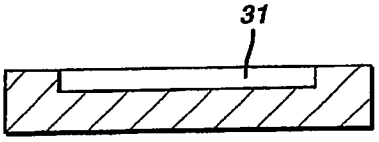
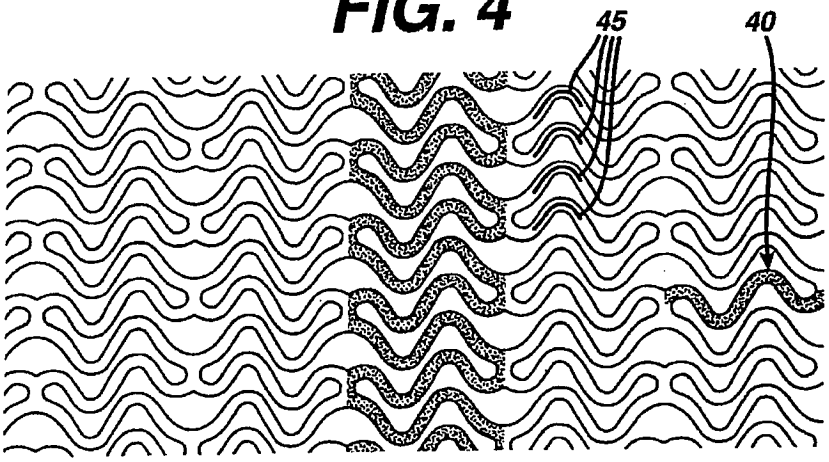


FIG. 4



STENT WITH THERAPEUTICALLY ACTIVE DOSAGE OF RAPAMYCIN COATED THEREON

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of U.S. application Ser. No. 09/061,568, filed Apr. 16, 1998, now issued as U.S. Pat. No. 6,273,913, which claims the benefit of U.S. Provisional Application No. 60/044,692, filed Apr. 18, 1997.

FIELD OF THE INVENTION

Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

BACKGROUND OF THE INVENTION

Re-narrowing (restenosis) of an artherosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10–50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft. While the exact hormonal and cellular processes promoting restenosis are still being determined, our present understanding is that the process of PTCA, besides opening the artherosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC). In response to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3–6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow.

Several recent experimental approaches to preventing SMC proliferation have shown promise althrough the mechanisms for most agents employed are still unclear. Heparin is the best known and characterized agent causing inhibition of SMC proliferation both in vitro and in animal models of balloon angioplasty-mediated injury. The mechanism of SMC inhibition with heparin is still not known but may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes c-fos and c-myc, 2) reduced cellular production of tissue plasminogen activator; are 3) binding and dequestration of growth regulatory factors such as fibrovalent growth factor (FGF).

Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers, angiotensin converting enzyme inhibitors (captopril, cilazapril), cyclosporir A, trapidil (an antianginal, antiplatelet agent), terbinafine (antifungal), colchicine and taxol (antitubulin antiproliferatives), and c-myc and c-myb antinsense oligonucleotides.

Additionally, a goat antibody to the SMC mitogen platelet derived growth factor (PDGF) has been shown to be effective in reducing myointimal thickening in a rat model of balloon angioplasty injury, thereby implicating PDGF directly in the etiology of restenosis. Thus, while no therapy has as yet proven successful clinically in preventing restenosis after angioplasty, the in vivo experimental success of several agents known to inhibit SMC growth suggests that these agents as a class have the capacity to prevent clinical restenosis and deserve careful evaluation in humans.

Coronary heart disease is the major cause of death in men over the age of 40 and in women over the age of fifty in the western world. Most coronary artery-related deaths are due to atherosclerosis. Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500,000–600,000 deaths in the United States annually. To arrest the disease process and prevent the more advanced disease states in which the cardiac muscle itself is compromised, direct intervention has been employed via percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG).

PTCA is a procedure in which a small balloon-tipped catheter is passed down a narrowed coronary artery and then expanded to re-open the artery. It is currently performed in approximately 250,000–300,000 patients each year. The major advantage of this therapy is that patients in which the procedure is successful need not undergo the more invasive surgical procedure of coronary artery bypass graft. A major difficulty with PTCA is the problem of post-angioplasty closure of the vessel, both immediately after PTCA (acute reocclusion) and in the long term (restenosis).

The mechanism of acute reocclusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus. Recently, intravascular stents have been examined as a means of preventing acute reclosure after PTCA.

Restenosis (chronic reclosure) after angioplasty is a more gradual process than acute reocclusion: 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty. While the exact mechanism for restenosis is still under active investigation, the general aspects of the restenosis process have been identified.

In the normal arterial will, smooth muscle cells (SMC) proliferate at a low rate (<0.1%/day; ref). SMC in vessel wall exists in a 'contractile' phenotype characterized by 80–90% of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, golgi bodies, and free ribosomes are few and located in the perinuclear region. Extracellular matrix surrounds SMC and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining SMC in the contractile phenotypic state.

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the arterial wall become injured. Cell derived growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), etc. released from platelets (i.e., PDGF) adhering to the damaged arterial luminal surface, invading macrophages and/or leukocytes, or directly from SMC (i.e., BFGF) provoke a proliferation and migratory response in medial SMC. These cells undergo a phenotypic change from the contractile phenotyope to a 'synthetic' phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum, golgi and free ribosomes. Proliferation/migration usually begins within 1–2 days post-

injury and peaks at 2 days in the media, rapidly declining thereafter (Campbell et al., In: *Vascular Smooth Muscle Cells in Culture,* Campbell, J. H. and Campbell, G. R., Eds, CRC Press, Boca Ration, 1987, pp. 39–55); Clowes, A. W. and Schwartz, S. M., Circ. Res. 56:139–145, 1985).

Finally, daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate. Proliferation and migration continues until the damaged luminal endothelial layer regenerates at which time proliferation ceases within the intima, usually within 7–14 days postinjury. The remaining increase in intimal thickening which occurs over the next 3–6 months is due to an increase in extracellular matrix rather than cell number. Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response. (Liu et al., Circulation, 79:1374–1387, 1989).

Patients with symptomatic reocclusion require either repeat PTCA or CABG. Because 30–50% of patients undergoing PTCA will experience restenosis, restenosis has clearly limited the success of PTCA as a therapeutic approach to coronary artery disease. Because SMC proliferation and migration are intimately involved with the pathophysiological response to arterial injury, prevention of SMC proliferation and migration represents a target for pharmacological intervention in the prevention of restenosis.

SUMMARY OF THE INVENTION

Novel Features and Applications to Stent Technology

Currently, attempts to improve the clinical performance of stents have involved some variation of either applying a coating to the metal, attaching a covering or membrane, or embedding material on the surface via ion bombardment. A stent designed to include reservoirs is a new approach which offers several important advantages over existing technologies.

Local Drug Delivery from a Stent to Inhibit Restenosis

In this application, it is desired to deliver a therapeutic agent to the site of arterial injury. The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent. The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks, and be as thin as possible so as to minimize the increase in profile. In addition, the coating material should not contribute to any adverse response by the body (i.e., should be non-thrombogenic, non-inflammatory, etc.). To date, the ideal coating material has not been developed for this application.

An alternative would be to design the stent to contain reservoirs which could be loaded with the drug. A coating or membrane of biocompatable material could be applied over the reservoirs which would control the diffusion of the drug from the reservoirs to the artery wall.

One advantage of this system is that the properties of the coating can be optimized for achieving superior biocompatibility and adhesion properties, without the addition requirement of being able to load and release the drug. The size, shape, position, and number of reservoirs can be used to control the amount of drug, and therefore the dose delivered.

DESCRIPTION OF THE DRAWINGS

The invention will be better understood in connection with the following figures in which

FIGS. **1** and **1***a* are top views and section views of a stent containing reservoirs as described in the present invention;

FIGS. **2***a* and **2***b* are similar views of an alternate embodiment of the stent with open ends;

FIGS. **3***a* and **3***b* are further alternate figures of a device containing a grooved reservoir; and

FIG. **4** is a layout view of a device containing a reservoir as in FIG. **3**.

DETAILED DESCRIPTION OF THE INVENTION

Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents. Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty. The calcium antagonists have also been unsuccessful in preventing restenosis, although they are still under study. Other agents currently under study include thromboxane inhibitors, prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al., 42 Ann. Rev. Med., 127–132 (1991); Popma et al., 84 *Circulation,* 1426–1436 (1991)).

Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements, thromboxane receptor antagonists, cholesterol lowering agents, and serotonin antagonists has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Franklin, S. M. and Faxon, D. P., 4 Coronary Artery Disease, 232–242 (1993); Serruys, P. W. et al., 88 *Circulation,* (part 1) 1588–1601, (1993).

Conversely, stents have proven useful in preventing reducing the proliferation of restenosis. Stents, such as the stent **40**, seen in layout in FIG. **4**, balloon-expandable slotted metal tubes (usually but not limited to stainless steel), which when expanded within the lumen of an angioplastied coronary artery, provide structural support to the arterial wall. This support is helpful in maintaining an open path for blood flow. In two randomized clinical trials, stents were shown to increase angiographic success after PTCA, increase the stenosed blood vessel lumen and to reduce the lesion recurrence at 6 months (Serruys et al., 331 New Eng Jour. Med, 495, (1994); Fischman et al., 331 New Eng Jour. Med. 496–501 (1994). Additionally, in a preliminary trial, heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Additionally, heparin coating appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 93 Circulation, 412–422 (1996). Thus, 1) sustained mechanical expansion of a stenosed coronary artery has been shown to provide some measure of restenosis prevention, and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs to local, injured tissue off the surface of the stent.

Numerous agents are being actively studied as antiproliferative agents for use in restenosis and have shown some

activity in experimental animal models. These include: heparin and heparin fragments (Clowes and Karnovsky, 265 *Nature,* 25–626, (1977); Guyton, J. R. et. al. 46 Circ. Res., 625–634, (1980); Clowes, A. W. and Clowes, M. M., 52 Lab. Invest., 611–616, (1985) A. W. and Clowes, M. M., 58 Circ. Res., 839–845 (1986); Majesky et al., 61 Circ Res., 296–300, (1987); Snow et al., 137 Am. J. Pathol., 313–330 (1990); Okada, T. et al., 25 *Neurosurgery,* 92–898, (1989) colchicine (Currier, J. W. et al., 80 *Circulation,* 11–66, (1989), taxol (ref), agiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., 245 Science, 186–188 (1989), angiopeptin (Lundergan, C. F. et al., 17 Am. J. Cardiol. (Suppl. B); 132B–136B (1991), Cyclosporin A (Jonasson, L. et. al., 85 Proc. Nati, Acad. Sci., 2303 (1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., 253 *Science,* 1129–1132 (1991), terbinafine (Nemecek, G. M. et al., 248 J. Pharmacol. Exp. Thera., 1167–11747 (1989), trapidil (Liu, M. W. et al., 81 *Circulation,* 1089–1093 (1990), interferon-gamma (Hansson, G. K. and Holm, 84 *J. Circulation,* 1266–1272 (1991), steroids (Colburn, M. D. et al., 15 J. Vasc. Surg., 510–518 (1992), see also Berk, B. C. et al., 17 J. Am. Coll. Cardiol., 111B–117B (1991), ionizing radiation (ref), fusion toxins (ref) antisense oligonucleotides (ref), gene vectors (ref), and rapamycin (see below).

Of particular interest in rapamycin. Rapamycin is a macrolide antibiotic which blocks IL-2-mediated T-cell proliferation and possesses antiinflammatory activity. While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G_1 to S phase progression of T-cells through the cell cycle by inhibiting specific cell cyclins and cyclin-dependent protein kinases (Siekierka, Immunol. Res. 13: 110–116, 1994). The antiproliferative action of rapamycin is not limited to T-cells; Marx et al. (Circ Res 76:412–417, 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC in vitro while Poon et al. have shown the rat, porcine, and human SMC migrating can also be inhibited by rapamycin (J Clin Invest 98: 2277–2283, 1996). Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response. In fact, the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al., Transplantation 55:1409–1418, 1993; Gallo et al., in press, (1997)). These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis.

Although the ideal agent for restenosis has not yet been identified, some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury, including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications. Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of SMC combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

Experiments

Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression.

Delivery Methods:

These can vary:

Local delivery of such agents (rapamycin) from the struts of a stent, from a stent graft, grafts, stent cover or sheath.

Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft.

or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein.

or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e.g. vapour deposition methods such as rf-plasma polymerization) and combinations thereof.

Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake

Extravascular delivery by the pericardial route

Extravascular delivery by the advential application of sustained release formulations.

Uses: for inhibition of cell proliferation to prevent neointimal proliferation and restenosis.

prevention of tumor expansion from stents

prevent ingrowth of tissue into catheters and shunts inducing their failure.

1. Experimental Stent Delivery Method—Delivery from Polymer Matrix

Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0.001 weight % to 30 weight % of drug. Polymers are biocompatible (i.e., not elicit any negative tissue reaction or promote mural thrombus formation) and degradable, such as lactone-based polyesters or copolyesters, e.g., polylactide, polycaprolactonglycolide,polyorthoesters, polyanhydrides; polyaminoacids; polysaccharides; polyphosphazenes; poly (ether-ester) copolymers, e.g., PEO-PLLA, or blends thereof. Nonabsorbable biocompatible polymers are also suitable candidates. Polymers such as polydimethylsiolxane; poly(ethylene-vingylacetate); acrylate based polymers or copolymers, e.g., poly(hydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters.

Polymer/drug mixture is applied to the surfaces of the stent by either dip-coating, or spray coating, or brush coating or dip/spin coating or combinations thereof, and the solvent allowed to evaporate to leave a film with entrapped rapamycin.

2. Experimental Stent Delivery Method—Delivery from Microporous Depots in Stent Through a Polymer Membrane Coating:

Stent, whose body has been modified to contain micropores or channels is dipped into a solution of Rapamycin, range 0.001 wt % to saturated, in organic solvent such as acetone or methylene chloride, for sufficient time to allow solution to permeate into the pores. (The dipping solution can also be compressed to improve the loading efficiency.) After solvent has been allowed to evaporate, the stent is dipped briefly in fresh solvent to remove excess surface bound drug. A solution of polymer, chosen from any identified in the first experimental method, is applied to the stent as detailed above. This outerlayer of polymer will act as diffusion-controller for release of drug.

3. Experimental Stent Delivery Method—Delivery Via Lysis of a Covalent Drug Tether

Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization. Covalent bonds such as ester, amides or anhydrides may be suitable for this.

4. Experimental Method—Pericardial Delivery

A: Polymeric Sheet Rapamycin is combined at concentration range previously highlighted, with a degradable polymer such as poly(caprolactone-gylcolide) or non-degradable polymer, e.g., polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10μ to 1000μ. The resulting sheet can be wrapped perivascularly on the target vessel. Preference would be for the absorbable polymer.

B: Conformal Coating: Rapamycin is combined with a polymer that has a melting temperature just above 37° C., range 40°–45° C. Mixture is applied in a molten state to the external side of the target vessel. Upon cooling to body temperature the mixture solidifies conformally to the vessel wall. Both non-degradable and absorbable biocompatible polymers are suitable.

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin. As seen in FIGS. **1***a*, **2***a* and **3***a*, any stent strut **10**, **20**, **30** can be modified to have a certain reservoir or channel **11**, **21**, **31**. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. FIG. **4** shows a stent **40** with a reservoir **45** created at the apex of a flexible strut. Of course, this reservoir **45** is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents.

In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must be kept at a size of about 0.0005" to about 0.003". Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

These and other concepts will are disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be perceived to fall within the scope of the invention which is to be realized from the attached claims and their equivalents.

What is claimed is:

1. A stent having a coating containing rapamycin, said coating formed from a polymer mixed carrier containing the rapamycin; and said coating applied to said stent.

2. The stent of claim **1** wherein the stent is dip-coated.

3. The stent of claim **1** wherein the stent is sprayed with said coating.

4. A stent having a coating containing rapamycin or its analogs, wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0.0001% to 30%.

5. The stent of claim **4** wherein a polymer is mixed to the rapamycin or its analogs.

6. The stent of claim **4** wherein a polymer is bound to the rapamycin or its analogs.

7. The stent of claim **4** wherein the rapamycin or its analogs is entrapped on the surface of the stent by a polymer.

8. A stent having a coating containing rapamycin, said coating formed from a polymer mixed carrier containing the rapamycin or its analogs; and said coating applied to said stent; wherein the polymer is biocompatible and degradable; and

wherein the polymer is chosen from: lactone-based polyesters, lactone-based copolyesters; polyanhydrides; polyaminoacids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, and blends of such polymers.

9. A stent having a coating containing rapamycin, said coating formed from a polymer mixed carrier containing the rapamycin or its analogs; and said coating applied to said stent; and

wherein the polymer is chosen from: lactone-based polyesters, lactone-based copolyesters; polyanhydrides; polyaminoacids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, and blends of such polymers.

10. A stent having a coating containing rapamycin, said coating formed from a polymer mixed carrier containing the rapamycin or its analogs; and said coating applied to said stent; wherein the polymer is nonabsorbable; and

wherein the polymer is chosen from: polydimethylsiolxane; poly(ethylene)vinylacetate; poly(hydroxy) ethylmethylmethacrylate, polyvinyl pyrrolidone; polytetrafluoroethylene; and cellulose esters.

11. A stent having a coating containing rapamycin or its analogs, said coating formed from a polymer mixed carrier containing the rapamycin or its analogs; and said coating applied to said stent; and

wherein the polymer is chosen from: polydimethylsiolxane; poly(ethylene)vinylacetate; poly(hydroxy) ethylmethylmethacrylate, polyvinyl pyrrolidone; polytetrafluoroethylene; and cellulose esters.

12. A stent having a coating containing rapamycin or its analogs, said coating formed from a polymer mixed carrier containing the rapamycin or its analogs; and said coating applied to said stent; and further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said applied to said strut, and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top, and said channel smaller in all dimensions than said strut, said channel containing a reservoir of said rapamycin coating applied therein.

13. A stent having a coating containing rapamycin or its analogs, wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0.0001% to 30%, wherein the coating is a polymer.

14. The stent of claim **13** wherein said polymer is mixed to the rapamycin or its analogs.

15. The stent of claim **4** wherein said polymer is bound to the rapamycin or its analogs.

16. The stent of claim **13** wherein the rapamycin or its analogs is entrapped on the surface of the stent by said polymer.

17. A stent containing a polymer and rapamycin or its analogs wherein said rapamycin or its analogs are contained in a therapeutically beneficial amount to combat restenosis.

18. The stent of claim **17** wherein said polymer is mixed to the rapamycin or its analogs.

19. The stent of claim **17** wherein said polymer is bound to the rapamycin or its analogs.

20. The stent of claim **17** wherein the rapamycin or its analogs is entrapped on the surface of the stent by said polymer.

* * * * *

Exhibit B

US006808536B2

(12) **United States Patent**
Wright et al.

(10) **Patent No.: US 6,808,536 B2**
(45) **Date of Patent: *Oct. 26, 2004**

(54) **STENT CONTAINING RAPAMYCIN OR ITS ANALOGS USING A MODIFIED STENT**

(76) Inventors: **Carol Wright**, 48 Marcy St., Somerset, NJ (US) 08873; **Gerard H. Llanos**, 1514 Mean Cir., Stewartsville, NJ (US) 08886; **Ronald Rakos**, 35 Regal Dr., Monmouth Jct, NJ (US); **Kristen King**, 51 Garden St., Apt. 611, Hoboken, NJ (US) 07030

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/408,328**

(22) Filed: **Apr. 7, 2003**

(65) **Prior Publication Data**

US 2003/0176915 A1 Sep. 18, 2003

Related U.S. Application Data

(63) Continuation of application No. 09/874,117, filed on Jun. 4, 2001, now Pat. No. 6,585,764, which is a continuation of application No. 09/061,568, filed on Apr. 16, 1998, now Pat. No. 6,273,913.

(60) Provisional application No. 60/044,692, filed on Apr. 18, 1997.

(51) **Int. Cl.**[7] **A61F 2/06**

(52) **U.S. Cl.** **623/1.42**

(58) **Field of Search** 623/1.15, 1.39, 623/1.42, 1.4; 427/2.1–2.31

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,234,456	A	8/1993	Silvestrini
5,282,823	A	2/1994	Schwartz et al.
5,283,257	A	2/1994	Gregory et al.
5,288,711	A	2/1994	Mitchell et al.
5,342,348	A	8/1994	Kaplan
5,383,928	A	1/1995	Scott et al.
5,443,496	A	8/1995	Schwartz et al.
5,449,382	A	9/1995	Dayton
5,464,450	A	11/1995	Buscemi et al.
5,464,650	A	11/1995	Berg et al.
5,500,013	A	3/1996	Buscemi et al.
5,510,077	A	4/1996	Dinh et al.
5,516,781	A	5/1996	Morris et al.
5,545,208	A	8/1996	Wolff et al.
5,551,954	A	9/1996	Buscemi et al.

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

EP	0 568 310 A	11/1993
EP	0 712 615	5/1996
EP	0 716 836	6/1996
EP	0 761 251 A	3/1997
EP	0 761 251	3/1997

(List continued on next page.)

OTHER PUBLICATIONS

Marx, Steven O. et al., Rapamycin–FKBP Inhibits Cell Cycle Regulators of Proliferation in Vascular Smooth Muscle Cells, Circulation Research, 1995;76(3):412–417.

Serruys, Patrick W. et al., Heparin–Coated Palmaz–Schatz Stents in Human Coronary Arteries, Circulation. 1996;93:412–422.

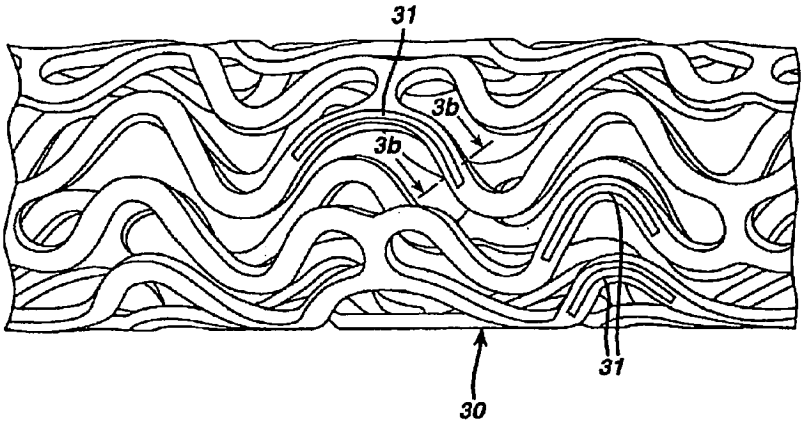
(List continued on next page.)

Primary Examiner—Suzette J. Jackson

(57) **ABSTRACT**

Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

6 Claims, 2 Drawing Sheets



U.S. PATENT DOCUMENTS

5,554,182	A		9/1996	Dinh et al.
5,562,922	A		10/1996	Lambert
5,563,146	A		10/1996	Morris et al.
5,571,166	A		11/1996	Dinh et al.
5,578,075	A		11/1996	Dayton
5,591,224	A		1/1997	Schwartz et al.
5,591,227	A		1/1997	Dinh et al.
5,599,352	A		2/1997	Dinh et al.
5,603,722	A		2/1997	Phan et al.
5,605,696	A		2/1997	Eury et al.
5,607,463	A		3/1997	Schwartz et al.
5,607,475	A		3/1997	Cahalan et al.
5,609,629	A		3/1997	Fearnot et al.
5,624,411	A		4/1997	Tuch
5,628,785	A		5/1997	Schwartz et al.
5,629,077	A		5/1997	Turnlund et al.
5,632,840	A		5/1997	Campbell
5,637,113	A		6/1997	Tartaglia et al.
5,646,160	A		7/1997	Morris et al.
5,649,977	A		7/1997	Campbell
5,651,174	A		7/1997	Schwartz et al.
5,672,638	A		9/1997	Verhoeven et al.
5,674,242	A		10/1997	Phan et al.
5,679,400	A		10/1997	Tuch
5,679,659	A		10/1997	Verhoeven et al.
5,693,085	A		12/1997	Buirge et al.
5,697,967	A		12/1997	Dinh et al.
5,700,286	A		12/1997	Tartaglia et al.
5,707,385	A		1/1998	Williams
5,725,567	A		3/1998	Wolff et al.
5,728,150	A		3/1998	McDonald et al.
5,728,420	A		3/1998	Keogh
5,733,327	A		3/1998	Igaki et al.
5,735,897	A		4/1998	Buirge
5,755,772	A		5/1998	Evans et al.
5,769,883	A		6/1998	Buscemi et al.
5,776,184	A		7/1998	Tuch
5,782,908	A		7/1998	Cahalan et al.
5,788,979	A		8/1998	Alt et al.
5,799,384	A		9/1998	Schwartz et al.
5,800,507	A		9/1998	Schwartz
5,820,917	A		10/1998	Tuch
5,820,918	A		10/1998	Ronan et al.
5,824,048	A		10/1998	Tuch
5,824,049	A		10/1998	Ragheb et al.
5,833,651	A		11/1998	Donovan et al.
5,837,008	A		11/1998	Berg et al.
5,837,313	A		11/1998	Ding et al.
5,843,172	A		12/1998	Yan
5,849,034	A		12/1998	Schwartz
5,851,217	A		12/1998	Wolff et al.
5,851,231	A		12/1998	Wolff et al.
5,865,814	A		2/1999	Tuch
5,871,535	A		2/1999	Wolff et al.
5,879,697	A		3/1999	Ding et al.
5,882,335	A		3/1999	Leone et al.
6,273,913	B1	*	8/2001	Wright et al. 623/1.42
6,517,889	B1	*	2/2003	Jayaraman 427/2.24
6,585,764	B2	*	7/2003	Wright et al. 623/1.42
2002/0068969	A1	*	6/2002	Shanley et al. 623/1.16
2002/0099438	A1	*	7/2002	Furst 623/1.16
2002/0123505	A1	*	9/2002	Mollison et al. 514/291
2003/0065377	A1	*	4/2003	Davila et al. 623/1.13

FOREIGN PATENT DOCUMENTS

EP	0 850 651		7/1998
EP	0 938 878	A2	9/1999
EP	0 938 878	A3	9/1999
EP	0 938 878	A	9/1999
EP	0 950 386	A	10/1999
WO	WO 96/32907		10/1996
WO	WO 97/33534	A1	9/1997
WO	WO 98/23228		6/1998
WO	WO 98/34669		8/1998
WO	WO 98/36784	A	8/1998
WO	WO 98/47447	A	10/1998
WO	WO 98/47447	A1	10/1998
WO	WO 98/56312		12/1998
WO	WO 00/21584	A1	4/2000
WO	WO 00/27445	A	5/2000
WO	WO 00/32255	A	6/2000
WO	WO 01/87342	A2	11/2001
WO	WO 02/26281	A1	4/2002
WO	WO 03/015664	A1	2/2003
WO	WO 03/057218	A1	7/2003

OTHER PUBLICATIONS

Lundergan, Conor F., MD et al., Peptide Inhibition of Myointimal Proliferation by Angiopeptin, a Somatostatin Analogue, JACC vol. 17, No. 6, May 1991:132B–6B.

Liu, Ming Wei, MD et al., Restenosis After Coronary Angioplasty Potential Biologic Determinants and Role of Intimal Hyperplasia, Circulation 1989, 79:1374–1387.

Serruys, P. W. et al., Evaulation of Ketanserin in the Prevention of Restenosis After Percutaneous Transluminal Coronary Angioplasty—A Multicenter Randomized Double–Blind Placbo–Controlled Trial, Circulartion vol. 88, No. 4, Part 1, Oct. 1993, 1588–1601.

Berk, Bradford C. MD et al., Pharmacologic Roles of Heparin and Glucocorticoids to Prevent Restenosis After Coronary Angioplasty, JACC vol. 17, No. 6, May 1991:111B–7B.

Serruys, Patrick W. MD et al. A Comparison of Balloon–Expandable–Stent Implantation with Balloon Angioplasty in Patients with Coronary Artery Disease, The New England Journal of Medicine, vol. 331, No. 8, Aug. 25, 1994, 489–495.

Fischman, David L. MD et al., A Randomized Comparison of Coronary–Stent Placement and Balloon Angioplasty in the Treatment of Coronary Artery Disease, The New England Journal of Medicine, vol. 331, No. 8, Aug. 25, 1994, 496–501.

Colburn, Michael D. MD et al., Dose Responsive suppression of myointimal hyperlasia by dexamethasone, Journal of Vascular Surgery, vol. 15, No. 3, Mar. 1992, 510–518.

Liu Ming, W. MD, Trapidil in Preventing Restenosis After Balloon Angioplasty in the Atherosclerotic Rabbit, Circulation, vol. 81, No. 3, Mar. 1990, 1089–1093.

Hansson, Goran K. MD, et al., Interferon—Inhibits Arterial Stenosis After Injury, Circulation, vol. 84, No. 3, Sept. 1991, 1266–1272.

Snow, Alan D. et al., Heparin Modulates the Composition of th Extracellular Matrix Domain Surrounding Arterial Smooth Muscle Cells, American Journal of Pathology, vol. 137, No. 2, Aug. 1990, 313–330.

Popma, Jeffrey J. MD et al., Clinical Trials of Restenosis After Coronary Angioplasty, Circulation vol. 84, No. 3, Sep. 1991, 1426–1436.

Campbell, Gordon R. et al., Phenotypic Modulation of Smooth Muscle Cells in Primary Culture, Vascular Smooth Muscle Cells in Culture, CRC Press 1987, pp39–55.

Clowes, Alexander W. et al., Significance of Quiescent Smooth Muscle Migration in the Injured Rat Carotid Artery, Cir Res 56: 139–145, 1985.

Lange, Richard A. MD et al., Restenosis After Coronary Balloon Angioplasty, Annu. Rev. Med. 1991, 42:127–32.
Franklin, Stephen, M. MD et al., Pharmacologic prevention of restenosis after coronary angioplasty: review of the randomized clinical trials, Coronary Artery Disease, Mar. 1993, vol. 4, No. 3, 232–242.
Suppression by heparin of smooth muscle cell proliferation in injured arteries, Nature, vol. 265, Feb. 17, 1977, 625–626–.
Guyton, John, R. et al., Inhibition of Rat Arterial Smooth Muscle Cell Proliferation by Heparin, Circulation Research, vol. 46, No. 5, May 1980, 625–634.
Clowes, Alexander W. et al., Kinetics of Cellular Proliferation after Arterial Injury, Circulation Research, vol. 58, No. 6, Jun. 1986, 839–845.
Majesky, Mark W., et al., Heparin Regulates Smooth Muscle S Phase Entry in the Injured Rat Carotid Artery, Circulation Research, vol. 61, No. 2, Aug. 1987, 296–300.
Okada, Tomohisa, MD et al., Localized Release of Perivascular Heparin Inhibits Intimal Proliferation after Endothelial Injury without Systematic Anticoagulation, Neurosurgery, vol. 25, No. 6, 1989, 892–898.
Vasey, Charles G. et al., Clinical Cardiology: Stress Echo and Coronary Flow, Supplement II Circulation, vol. 80, No. 4, Oct. 1989, 11–66.
Powell, Jerry S. et al., Inhibitors of Angiotensin–Converting Enzyme Prevent Myointimal Proliferation After Vascular Injury, Science, vol. 245, Jul. 14, 1989, 186–188.
Jonasson, Lena et al, Cyclosporin A inhibits smooth muscle proliferation in the vascular response to injury, Proc. Natl. Acad. Sci USA 85 (1988), pp 2303–2306.
Nemecek, Georgina M. et al., Terbinafine Inhibits the Mitogenic Response to Platelet–Derived Growth Factor in Vitro and Neointimal Proliferation in Vivo, The Journal of Pharmacology and Experimental Therapeutics, vol. 248, No. 3, 1998, 1167–1174.
Siekierka, John J., Probing T–Cell Signal Transduction Pathways with the Immunosuppressive Drugs, FK–506 and Rapamycin, Immunologic Research 1994, 13:110–116.
Poon, Michael et al., Rapamycin Inhibits Vascular Smooth Muscle Cell Migration, J. Clin. Invest., vol. 98, No. 10, Nov 1996, 2277–2283.
Gregory, Clare R. et al., Rapamycin Inhibits Arterial Intimal Thickening Caused by Both Alloimmune and Mechanical Injury, Transplantation vol. 55, No. 6, Jun. 1993, 1409–1418.
European Search Report dated Sep. 22, 2003 for corresponding Appln. No. EP 03 25 2350.

* cited by examiner

FIG. 1

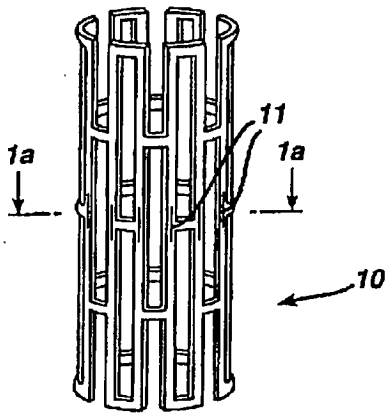


FIG. 1a

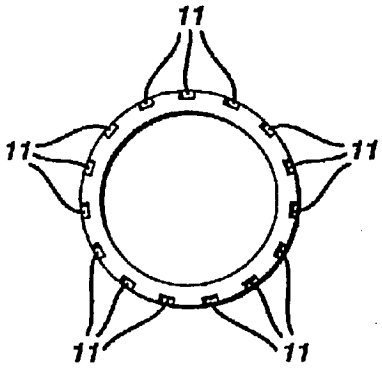


FIG. 2a

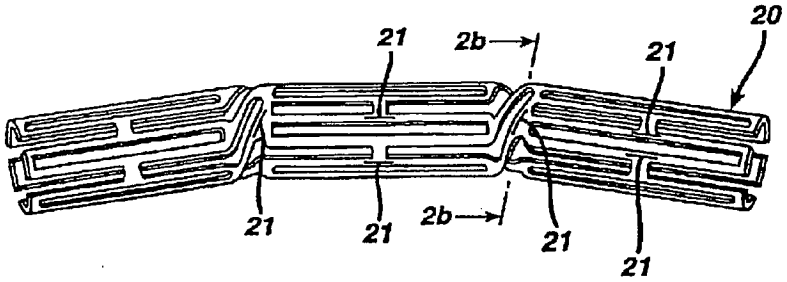


FIG. 2b

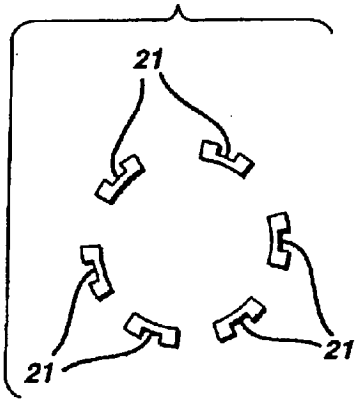


FIG. 3a

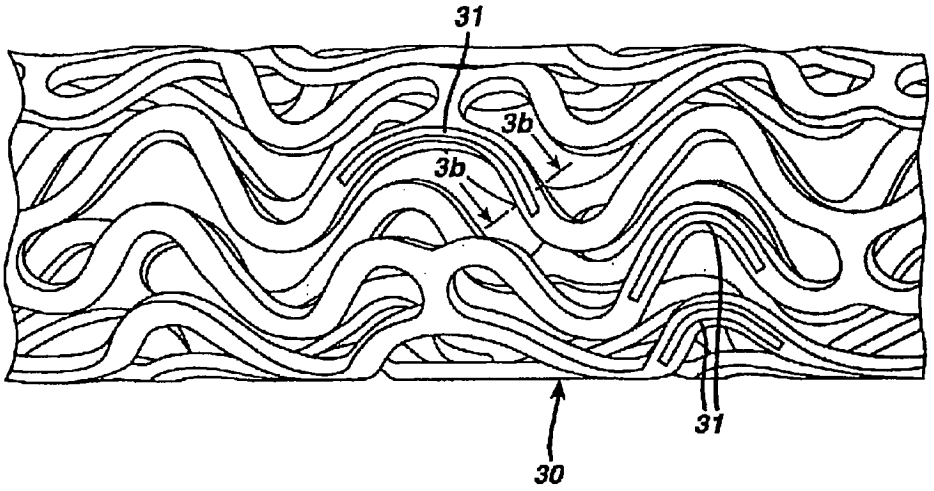


FIG. 3b

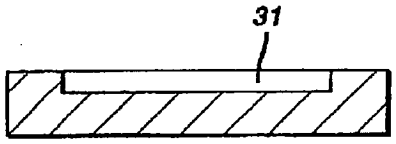
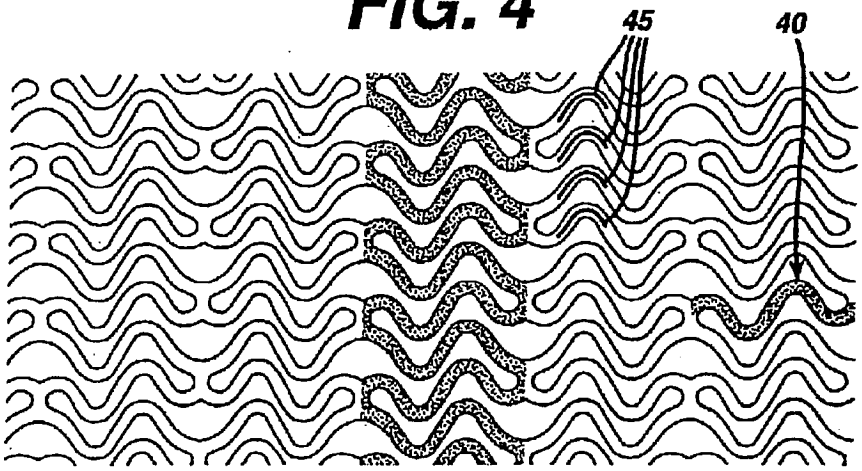


FIG. 4



STENT CONTAINING RAPAMYCIN OR ITS ANALOGS USING A MODIFIED STENT

Continuation of prior application Ser. No.: 09/874,117, filed Jun. 4, 2001, now U.S. Pat. No. 6,585,764 which is a continuation of Ser. No. 09/061,568 filed Apr. 16, 1998, now U.S. Pat. No. 6,273,913; which claim the benefit of U.S. Provisional Application No. 60/044,692, filed Apr. 18, 1997.

FIELD OF THE INVENTION

Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

BACKGROUND OF THE INVENTION

Re-narrowing (restenosis) of an artherosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10–50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft. While the exact hormonal and cellular processes promoting restenosis are still being determined, our present understanding is that the process of PTCA, besides opening the artherosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC). In response to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3–6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow.

Several recent experimental approaches to preventing SMC proliferation have shown promise althrough the mechanisms for most agents employed are still unclear. Heparin is the best known and characterized agent causing inhibition of SMC proliferation both in vitro and in animal models of balloon angioplasty-mediated injury. The mechanism of SMC inhibition with heparin is still not known but may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes c-fos and c-myc, 2) reduced cellular production of tissue plasminogen activator; are 3) binding and dequestration of growth regulatory factors such as fibrovalent growth factor (FGF).

Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers, angiotensin converting enzyme inhibitors (captopril, cilazapril), cyclosporin A, trapidil (an antianginal, antiplatelet agent), terbinafine (antifungal), colchicine and taxol (antitubulin antiproliferatives), and c-myc and c-myb antinsense oligonucleotides.

Additionally, a goat antibody to the SMC mitogen platelet derived growth factor (PDGF) has been shown to be effective in reducing myointimal thickening in a rat model of balloon angioplasty injury, thereby implicating PDGF directly in the etiology of restenosis. Thus, while no therapy has as yet proven successful clinically in preventing restenosis after angioplasty, the in vivo experimental success of several agents known to inhibit SMC growth suggests that these agents as a class have the capacity to prevent clinical restenosis and deserve careful evaluation in humans.

Coronary heart disease is the major cause of death in men over the age of 40 and in women over the age of fifty in the western world. Most coronary artery-related deaths are due to atherosclerosis. Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500,000–600,000 deaths in the United States annually. To arrest the disease process and prevent the more advanced disease states in which the cardiac muscle itself is compromised, direct intervention has been employed via percutaneous transiuminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG).

PTCA is a procedure in which a small balloon-tipped catheter is passed down a narrowed coronary artery and then expanded to re-open the artery. It is currently performed in approximately 250,000–300,000 patients each year. The major advantage of this therapy is that patients in which the procedure is successful need not undergo the more invasive surgical procedure of coronary artery bypass graft. A major difficulty with PTCA is the problem of post-angioplasty closure of the vessel, both immediately after PTCA (acute reocclusion) and in the long term (restenosis).

The mechanism of acute reocclusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus. Recently, intravascular stents have been examined as a means of preventing acute reclosure after PTCA.

Restenosis (chronic reclosure) after angioplasty is a more gradual process than acute reocclusion: 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty. While the exact mechanism for restenosis is still under active investigation, the general aspects of the restenosis process have been identified:

In the normal arterial will, smooth muscle cells (SMC) proliferate at a low rate (<0.1%/day; ref). SMC in vessel wall exists in a 'contractile' phenotype characterized by 80–90% of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, golgi bodies, and free ribosomes are few and located in the perinuclear region. Extracellular matrix surrounds SMC and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining SMC in the contractile phenotypic state.

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the arterial wall become injured. Cell derived growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), etc. released from platelets (i.e., PDGF) adhering to the damaged arterial luminal surface, invading macrophages and/or leukocytes, or directly from SMC (i.e., BFGF) provoke a proliferation and migratory response in medial SMC. These cells undergo a phenotypic change from the contractile phenotyope to a 'synthetic' phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum, golgi and free ribosomes. Proliferation/migration usually begins within 1–2 days post-injury and peaks at 2 days in the media, rapidly declining thereafter (Campbell et al., In: *Vascular Smooth Muscle Cells in Culture*, Campbell, J. H. and Campbell, G. R., Eds, CRC Press, Boca Ration, 1987, pp. 39–55); Clowes, A. W. and Schwartz, S. M., Circ. Res. 56:139–145, 1985).

Finally, daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate. Proliferation and migration continues until the damaged luminal endothelial layer regenerates at which time proliferation ceases within the intima, usually within 7–14 days postinjury. The remaining increase in intimal thickening which occurs over the next 3–6 months is due to an increase in extracellular matrix rather than cell number. Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response. (Liu et al., Circulation, 79:1374–1387, 1989).

Patients with symptomatic reocclusion require either repeat PTCA or CABG. Because 30–50% of patients undergoing PTCA will experience restenosis, restenosis has clearly limited the success of PTCA as a therapeutic approach to, coronary artery disease. Because SMC proliferation and migration are intimately involved with the pathophysiological response to arterial injury, prevention of SMC proliferation and migration represents a target for pharmacological intervention in the prevention of restenosis.

SUMMARY OF THE INVENTION

Novel Features and Applications to Stent Technology

Currently, attempts to improve the clinical performance of stents have involved some variation of either applying a coating to the metal, attaching a covering or membrane, or embedding material on the surface via ion bombardment. A stent designed to include reservoirs is a new approach which offers several important advantages over existing technologies.

Local Drug Delivery from a Stent to Inhibit Restenosis

In this application, it is desired to deliver a therapeutic agent to the site of arterial injury. The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent. The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks, and be as thin as possible so as to minimize the increase in profile. In addition, the coating material should not contribute to any adverse response by the body (i.e., should be non-thrombogenic, non-inflammatory, etc.). To date, the ideal coating material has not been developed for this application.

An alternative would be to design the stent to contain reservoirs which could be loaded with the drug. A coating or membrane of biocompatable material could be applied over the reservoirs which would control the diffusion of the drug from the reservoirs to the artery wall.

One advantage of this system is that the properties of the coating can be optimized for achieving superior biocompatibility and adhesion properties, without the addition requirement of being able to load and release the drug. The size, shape, position, and number of reservoirs can be used to control the amount of drug, and therefore the dose delivered.

DESCRIPTION OF THE DRAWINGS

The invention will be better understood in connection with the following figures in which

FIGS. **1** and **1A** are top views and section views of a stent containing reservoirs as described in the present invention;

FIGS. **2***a* and **2***b* are similar views of an alternate embodiment of the stent with open ends;

FIGS. **3***a* and **3***b* are further alternate figures of a device containing a grooved reservoir; and

FIG. **4** is a layout view of a device containing a reservoir as in FIG. **3**.

DETAILED DESCRIPTION OF THE INVENTION

Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents. Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty. The calcium antagonists have also been unsuccessful in preventing restenosis, although they are still under study. Other agents currently under study include thromboxane inhibitors, prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al., 42 Ann. Rev. Med., 127–132 (1991); Popma et al., 84 *Circulation*, 1426–1436 (1991)).

Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements, thromboxane receptor antagonists, cholesterol lowering agents, and serotonin antagonists has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Franklin, S. M. and Faxon, D. P., 4 Coronary Artery Disease, 232–242 (1993); Serruys, P. W. et al., 88 *Circulation*, (part 1) 1588–1601, (1993).

Conversely, stents have proven useful in preventing reducing the proliferation of restenosis. Stents, such as the stent **10** seen in layout in FIG. **4**, balloon-expandable slotted metal tubes (usually but not limited to stainless steel), which when expanded within the lumen of an angioplastied coronary artery, provide structural support to the arterial wall. This support is helpful in maintaining an open path for blood flow. In two randomized clinical trials, stents were shown to increase angiographic success after PTCA, increase the stenosed blood vessel lumen and to reduce the lesion recurrence at 6 months (Serruys et al., 331 New Eng Jour. Med, 495, (1994); Fischman et al., 331 New Eng Jour. Med, 496–501 (1994). Additionally, in a preliminary trial, heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Additionally, heparin coating appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 93 Circulation, 412–422, (1996). Thus, 1) sustained mechanical expansion of a stenosed coronary artery has been shown to provide some measure of restenosis prevention, and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs to local, injured tissue off the surface of the stent.

Numerous agents are being actively studied as antiproliferative agents for use in restenosis and have shown some activity in experimental animal models. These include: heparin and heparin fragments (Clowes and Karnovsky, 265 Nature, 25–626, (1977); Guyton, J. R. et al. 46 Circ. Res., 625–634, (1980); Clowes, A. W. and Clowes, M. M., 52 Lab.

Invest., 611–616, (1985); Clowes, A. W. and Clowes, M. M., 58 Circ. Res., 839–845 (1986); Majesky et al., 61 Circ Res., 296–300, (1987); Snow et al., 137 Am. J. Pathol., 313–330 (1990); Okada, T. et al., 25 *Neurosurgery,* 92–898, (1989) colchicine (Currier, J. W. et al., 80 *Circulation,* 11–66, (1989), taxol (ref), agiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., 245 Science, 186–188 (1989), angiopeptin (Lundergan, C. F. et al., 17 Am. J. Cardiol. (Suppl. B); 132B–136B (1991), Cyclosporin A (Jonasson, L. et. al., 85 Proc. Nati, Acad. Sci., 2303 (1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., 253 Science, 1129–1132 (1991), terbinafine (Nemecek, G. M. et al., 248 J. Pharmacol. Exp. Thera., 1167–11747 (1989), trapidil (Liu, M. W. et al., 81 *Circulation,* 1089–1093 (1990), interferon-gamma (Hansson, G. K. and Holm, 84 J. Circulation, 1266–1272 (1991), steroids (Colburn, M. D. et al., 15 J. Vasc. Surg., 510–518 (1992), see also Berk, B. C. et al., 17 J. Am. Coll. Cardiol., 111B–117B (1991), ionizing radiation (ref), fusion toxins (ref) antisense oligonucleotides (ref), gene vectors (ref), and rapamycin (see below).

Of particular interest in rapamycin. Rapamycin is a macrolide antibiotic which blocks IL-2-mediated T-cell proliferation and possesses antiinflammatory activity. While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G_1 to S phase progression of T-cells through the cell cycle by inhibiting specific cell cyclins and cyclin-dependent protein kinases (Siekierka, Immunol. Res. 13: 110–116, 1994). The antiproliferative action of rapamycin is not limited to T-cells; Marx et al. (Circ Res 76:412–417, 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC in vitro while Poon et al. have shown the rat, porcine, and human SMC migratin can also be inhibited by rapamycin (J Clin Invest 98: 2277–2283, 1996). Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response. In fact, the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in a rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al., Transplantation 55:1409–1418, 1993; Gallo et al., in press, (1997)). These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis.

Although the ideal agent for restenosis has not yet been identified, some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury, including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications. Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of SMC combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

Experiments

Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression.

Delivery Methods:

These can vary:

Local delivery of such agents (rapamycin) from the struts of a stent, from a stent graft, grafts, stent cover or sheath.

Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft.

or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein.

or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e.g. vapour deposition methods such as rf-plasma polymerization) and combinations thereof.

Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake

Extravascular delivery by the pericardial route

Extravascular delivery by the advential application of sustained release formulations.

Uses: for inhibition of cell proliferation to prevent neointimal proliferation and restenosis.

prevention of tumor expansion from stents

prevent ingrowth of tissue into catheters and shunts inducing their failure.

1. Experimental Stent Delivery Method—Delivery from Polymer Matrix:

Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0.001 weight % to 30 weight % of drug. Polymers are biocompatible (i.e., not elicit any negative tissue reaction or promote mural thrombus formation) and degradable, such as lactone-based polyesters or copolyesters, e.g., polylactide, polycaprolactonglycolide, polyorthoesters, polyanhydrides; polyaminoacids; polysaccharides; polyphosphazenes; poly (ether-ester) copolymers, e.g., PEO-PLLA, or blends thereof. Nonabsorbable biocompatible polymers are also suitable candidates. Polymers such as polydimethylsiolxane; poly(ethylene-vingylacetate); acrylate based polymers or copolymers, e.g., poly(hydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters.

Polymer/drug mixture is applied to the surfaces of the stent by either dip-coating, or spray coating, or brush coating or dip/spin coating or combinations thereof, and the solvent allowed to evaporate to leave a film with entrapped rapamycin.

2. Experimental Stent Delivery Method—Delivery from Microporous Depots in Stent Through a Polymer Membrane Coating:

Stent, whose body has been modified to contain micropores or channels is dipped into a solution of Rapamycin, range 0.001 wt % to saturated, in organic solvent such as acetone or methylene chloride, for sufficient time to allow solution to permeate into the pores. (The dipping solution can also be compressed to improve the loading efficiency.) After solvent has been allowed to evaporate, the stent is dipped briefly in fresh solvent to remove excess surface bound drug. A solution of polymer, chosen from any identified in the first experimental method, is applied to the stent as detailed above. This outerlayer of polymer will act as diffusion-controller for release of drug.

3. Experimental Stent Delivery Method—Delivery via Lysis of a Covalent Drug Tether

Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization. Covalent bonds such as ester, amides or anhydrides may be suitable for this.

4. Experimental Method—Pericardial Delivery

A: Polymeric Sheet Rapamycin is combined at concentration range previously highlighted, with a degradable

polymer such as poly(caprolactone-gylcolide) or non-degradable polymer, e.g., polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10μ to 1000 μ. The resulting sheet can be wrapped perivascularly on the target vessel. Preference would be for the absorbable polymer.

B: Conformal Coating: Rapamycin is combined with a polymer that has a melting temperature just above 37° C., range 40°–45° C. Mixture is applied in a molten state to the external side of the target vessel. Upon cooling to body temperature the mixture solidifies conformally to the vessel wall. Both non-degradable and absorbable biocompatible polymers are suitable.

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin. As seen in FIGS. **1***a*, **2***a* and **3***a*, any stent strut **10**, **20**, **30** can be modified to have a certain reservoir or channel **11**, **21**, **31**. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. FIG. **4** shows a stent **40** with a reservoir **45** created at the apex of a flexible strut. Of course, this reservoir **45** is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents.

In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must be kept at a size of about 0.0005" to about 0.003". Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

These and other concepts will are disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be perceived to fall within the scope of the invention which is to be realized from the attached claims and their equivalents.

What is claimed is:

1. A stent having a coating containing rapamycin or its analogs, wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0.0001% to 30%, said stent further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said coating applied to said strut, and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top, and said channel smaller in all dimensions than said strut, said channel containing a reservoir of said rapamycin containing coating applied therein.

2. A stent having a coating containing rapamycin or its analogs, wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0.0001% to 30%, wherein the coating is a polymers said stent further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said coating applied to said strut, and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top, and said channel smaller in all dimensions than said strut, said channel containing a reservoir of said rapamycin containing coating applied therein.

3. A stent containing a polymer and rapamycin or its analogs wherein said rapamycin or its analogs are contained in a therapeutically beneficial amount to combat restenosis, said stent further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said coating applied to said strut, and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top, and said channel smaller in all dimensions than said strut, said channel containing a reservoir of said rapamycin containing coating applied therein.

4. A stent having a coating containing rapamycin or its analogs, wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0.0001% to 30%, said stent further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said coating applied to said struts.

5. A stent having a coating containing rapamycin or its analogs, wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0.0001% to 30%, wherein the coating is a polymer, said stent further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said coating applied to said struts.

6. A stent containing a polymer and rapamycin or its analogs wherein said rapamycin or its analogs are contained in a therapeutically beneficial amount to combat restenosis, said stent further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said coating applied to said struts.

* * * * *

Exhibit C

US006776796B2

(12) **United States Patent**
Falotico et al.

(10) **Patent No.: US 6,776,796 B2**
(45) **Date of Patent: Aug. 17, 2004**

(54) **ANTIINFLAMMATORY DRUG AND DELIVERY DEVICE**

(75) Inventors: **Robert Falotico**, Belle Mead, NJ (US); **Gregory A. Kopia**, Neshanic, NJ (US); **Gerard H. Llanos**, Stewartsville, NJ (US); **John Siekierka**, Towaco, NJ (US); **Andrew J. Carter**, Portland, OR (US)

(73) Assignee: **Cordis Corportation**, Miami Lakes, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 129 days.

(21) Appl. No.: **09/850,232**

(22) Filed: **May 7, 2001**

(65) **Prior Publication Data**

US 2002/0016625 A1 Feb. 7, 2002

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/575,480, filed on May 19, 2000.

(60) Provisional application No. 60/263,979, filed on Jan. 25, 2001, provisional application No. 60/263,806, filed on Jan. 24, 2001, provisional application No. 60/262,614, filed on Jan. 18, 2001, provisional application No. 60/262,461, filed on Jan. 18, 2001, and provisional application No. 60/204,417, filed on May 12, 2000.

(51) **Int. Cl.**[7] **A61F 2/06**

(52) **U.S. Cl.** **623/1.46**

(58) **Field of Search** 623/1.42, 1.43, 623/1.44, 1.45, 1.46

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,657,744	A	4/1972	Ersek
3,932,627	A	1/1976	Margraf
4,292,965	A	10/1981	Nash et al.
4,441,216	A	4/1984	Ionescu et al.
4,503,569	A	3/1985	Dotter
4,553,545	A	11/1985	Maass et al.
4,580,568	A	4/1986	Gianturco
4,613,665	A	9/1986	Larm
4,655,771	A	4/1987	Wallsten
4,733,665	A	3/1988	Palmaz
4,739,762	A	4/1988	Palmaz
4,776,337	A	10/1988	Palmaz
4,800,882	A	1/1989	Gianturco
4,856,516	A	8/1989	Hillstead
4,872,867	A	10/1989	Joh

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

DE	3205942 A1	9/1983
EP	540290 A2	10/1992
EP	568 310 A1	11/1993

(List continued on next page.)

OTHER PUBLICATIONS

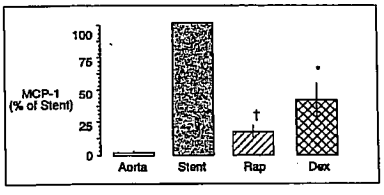
Ruef, Johannes Md, et al.; "Flavopiridol Inhibits Smooth Muscle Cell Proliferation In Vitro and Neointimal Formation In Vivo After Carotid Injury In the Rat"; From the Division of Cardiology and Sealy Center for Molecular Cardiology, University of Texas Medical Branch, Galveston; Accepted Apr. 9, 1999; Circulation Aug. 10, 1999; pp 659–665.

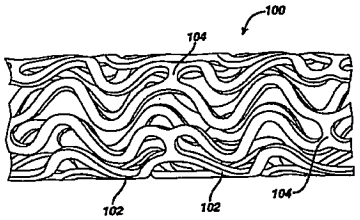
Primary Examiner—Manuel Mendez
Assistant Examiner—Mark K. Han
(74) *Attorney, Agent, or Firm*—Carl J. Evens

(57) **ABSTRACT**

A drug and drug delivery system may be utilized in the treatment of vascular disease. A local delivery system is coated with rapamycin or other suitable drug, agent or compound and delivered intraluminally for the treatment and prevention of neointimal hyperplasia following percutaneous transluminal coronary angiography. The local delivery of the drugs or agents provides for increased effectiveness and lower systemic toxicity.

11 Claims, 2 Drawing Sheets





U.S. PATENT DOCUMENTS

4,886,062	A	12/1989	Wiktor
4,907,336	A	3/1990	Gianturco
4,916,193	A	4/1990	Tang et al.
4,954,126	A	9/1990	Wallsten
4,969,458	A	11/1990	Wiktor
4,990,131	A	2/1991	Dardik
4,990,155	A	2/1991	Wilkoff
4,994,071	A	2/1991	MacGregor
5,015,253	A	5/1991	MacGregor
5,035,706	A	7/1991	Gianturco
5,041,100	A	8/1991	Rowland et al.
5,041,126	A	8/1991	Gianturco
5,049,132	A	9/1991	Shaffer et al.
5,053,048	A	10/1991	Pinchuk
5,061,275	A	10/1991	Wallsten et al.
5,061,750	A	10/1991	Feijen et al.
5,064,435	A	11/1991	Porter
5,092,877	A	3/1992	Pinchuk
5,102,417	A	4/1992	Palmaz
5,104,404	A	4/1992	Wolff
5,116,365	A	5/1992	Hillstead
5,122,154	A	6/1992	Rhodes
5,131,908	A	7/1992	Dardik et al.
5,133,732	A	7/1992	Wiktor
5,134,192	A	7/1992	Feijen et al.
5,135,536	A	8/1992	Hillstead
5,163,952	A	11/1992	Froix
5,163,958	A	11/1992	Pinchuk
5,171,262	A	12/1992	MacGregor
5,176,660	A	1/1993	Truckai
5,178,618	A	1/1993	Kandarpa
5,180,366	A	1/1993	Woods
5,182,317	A	1/1993	Winters et al.
5,185,408	A	2/1993	Tang et al.
5,192,307	A	3/1993	Wall
5,195,984	A	3/1993	Schatz
5,213,576	A	5/1993	Abiuso et al.
5,217,483	A	6/1993	Tower
5,222,971	A	6/1993	Willard et al.
5,226,913	A	7/1993	Pinchuk
5,234,456	A	8/1993	Silvestrini
5,246,445	A	9/1993	Yachia et al.
5,258,020	A	11/1993	Froix
5,258,021	A	11/1993	Duran
5,262,451	A	11/1993	Winters et al.
5,266,073	A	11/1993	Wall
5,275,622	A	1/1994	Lazarus et al.
5,282,823	A	2/1994	Schwartz et al.
5,282,824	A	2/1994	Gianturco
5,283,257	A	2/1994	Gregory et al.
5,288,711	A	2/1994	Mitchell et al.
5,290,305	A	3/1994	Inoue
5,292,331	A	3/1994	Boneau
5,292,802	A	3/1994	Rhee et al.
5,304,121	A	4/1994	Sahatjian
5,304,200	A	4/1994	Spaulding
5,306,250	A	4/1994	March et al.
5,308,862	A	5/1994	Ohlstein
5,308,889	A	5/1994	Rhee et al.
5,314,444	A	5/1994	Gianturco
5,314,472	A	5/1994	Fontaine
5,328,471	A	7/1994	Slepian
5,334,301	A	8/1994	Heinke et al.
5,336,518	A	8/1994	Narayanan et al.
5,338,770	A	8/1994	Winters et al.
5,342,348	A	8/1994	Kaplan
5,342,387	A	8/1994	Summers
5,342,621	A	8/1994	Eury
5,354,257	A	10/1994	Roubin et al.
5,354,308	A	10/1994	Simon et al.
5,356,433	A	10/1994	Rowland et al.
5,366,504	A	11/1994	Andersen et al.
5,368,566	A	11/1994	Crocker
5,370,683	A	12/1994	Fontaine
5,370,691	A	12/1994	Samson
5,375,612	A	12/1994	Cottenceau et al.
5,376,112	A	12/1994	Duran
5,380,299	A	1/1995	Fearnot et al.
5,382,261	A	1/1995	Palmaz
5,383,928	A	1/1995	Scott et al.
5,387,235	A	2/1995	Chuter
5,389,106	A	2/1995	Tower
5,393,772	A	2/1995	Yue et al.
5,395,390	A	3/1995	Simon et al.
5,397,355	A	3/1995	Marin et al.
5,403,341	A	4/1995	Solar
5,405,377	A	4/1995	Cragg
5,409,696	A	4/1995	Narayanan et al.
5,411,549	A	5/1995	Peters
5,415,619	A	5/1995	Lee et al.
5,419,760	A	5/1995	Narciso, Jr.
D359,802	S	6/1995	Fontaine
5,421,955	A	6/1995	Lau
5,423,885	A	6/1995	Williams
5,429,618	A	7/1995	Keogh
5,429,634	A	7/1995	Narciso
5,439,446	A	8/1995	Barry
5,441,515	A	8/1995	Khosravi et al.
5,441,516	A	8/1995	Wang et al.
5,441,947	A	8/1995	Dodge et al.
5,443,458	A	8/1995	Eury
5,443,477	A	8/1995	Marin et al.
5,443,496	A	8/1995	Schwartz et al.
5,443,498	A	8/1995	Fontaine
5,443,500	A	8/1995	Sigwart
5,447,724	A	9/1995	Helmus et al.
5,449,372	A	9/1995	Schmaltz et al.
5,449,373	A	9/1995	Pinchasik et al.
5,449,382	A	9/1995	Dayton
5,464,450	A	11/1995	Buscemi et al.
5,464,650	A	11/1995	Berg et al.
5,486,357	A	1/1996	Narayanan
5,496,365	A	3/1996	Sgro
5,500,013	A	3/1996	Buscemi et al.
5,510,077	A	4/1996	Dinh et al.
5,516,781	A	5/1996	Morris et al.
5,519,042	A	5/1996	Morris et al.
5,523,092	A	6/1996	Hanson et al.
5,527,354	A	6/1996	Fontaine et al.
5,545,208	A	8/1996	Wolff et al.
5,551,954	A	9/1996	Buscemi et al.
5,554,182	A	9/1996	Dinh et al.
5,554,954	A	9/1996	Takahashi
5,556,413	A	9/1996	Lam
5,562,922	A	10/1996	Lambert
5,563,146	A	10/1996	Morris et al.
5,569,197	A	10/1996	Helmus et al.
5,569,295	A	10/1996	Lam
5,569,462	A	10/1996	Martinson et al.
5,571,166	A	11/1996	Dinh et al.
5,574,059	A	11/1996	Regunathan et al.
5,578,075	A	11/1996	Dayton
5,580,873	A	12/1996	Bianco et al.
5,580,874	A	12/1996	Bianco et al.
5,591,140	A	1/1997	Narayanan et al.
5,591,197	A	1/1997	Orth et al.
5,591,224	A	1/1997	Schwartz et al.
5,591,227	A	1/1997	Dinh et al.
5,599,352	A	2/1997	Dinh et al.
5,603,722	A	2/1997	Phan et al.
5,605,696	A	2/1997	Eury et al.

5,607,463 A	3/1997	Schwartz et al.	
5,607,475 A	3/1997	Cahalan et al.	
5,609,629 A	3/1997	Fearnot et al.	
5,620,984 A	4/1997	Bianco et al.	
5,621,102 A	4/1997	Bianco et al.	
5,622,975 A	4/1997	Singh et al.	
5,624,411 A	4/1997	Tuch	
5,628,785 A	5/1997	Schwartz et al.	
5,629,077 A	5/1997	Turnlund et al.	
5,629,315 A	5/1997	Bianco et al.	
5,632,763 A	5/1997	Glastra	
5,632,840 A	5/1997	Campbell	
5,637,113 A	6/1997	Tartaglia et al.	
5,643,312 A	7/1997	Fischell et al.	
5,643,939 A	7/1997	Ohlstein	
5,646,160 A	7/1997	Morris et al.	
5,648,357 A	7/1997	Bianco et al.	
5,649,952 A	7/1997	Lam	
5,649,977 A	7/1997	Campbell	
5,651,174 A	7/1997	Schwartz et al.	
5,652,243 A	7/1997	Bianco et al.	
5,653,992 A	8/1997	Bezwada et al.	
5,662,609 A	9/1997	Slepian	
5,665,728 A	9/1997	Morris et al.	
5,669,924 A	9/1997	Shaknovich	
5,670,506 A	9/1997	Leigh et al.	
5,672,638 A	9/1997	Verhoeven et al.	
5,674,242 A	10/1997	Phan et al.	
5,679,400 A	10/1997	Tuch	
5,679,659 A	10/1997	Verhoeven et al.	
5,693,085 A	12/1997	Buirge et al.	
5,697,967 A	12/1997	Dinh et al.	
5,697,971 A	12/1997	Fischell et al.	
5,700,286 A	12/1997	Tartaglia et al.	
5,707,385 A	1/1998	Williams	
5,709,874 A	1/1998	Hanson et al.	
5,725,549 A	3/1998	Lam	
5,725,567 A	3/1998	Wolff et al.	
5,728,150 A	3/1998	McDonald et al.	
5,728,420 A	3/1998	Keogh	
5,731,326 A	3/1998	Hart et al.	
5,733,327 A	3/1998	Igaki et al.	
5,733,920 A	3/1998	Mansuri et al.	
5,733,925 A	3/1998	Kunz et al.	
5,735,897 A	4/1998	Buirge	
5,739,138 A	4/1998	Bianco et al.	
5,755,734 A	5/1998	Richter et al.	
5,755,772 A	5/1998	Evans et al.	
5,769,883 A	6/1998	Buscemi et al.	
5,776,184 A	7/1998	Tuch	
5,780,476 A	7/1998	Underiner et al.	
5,782,908 A	7/1998	Cahalan et al.	
5,788,979 A	8/1998	Alt et al.	
5,792,772 A	8/1998	Bianco et al.	
5,798,372 A	8/1998	Davies et al.	
5,799,384 A	9/1998	Schwartz et al.	
5,800,507 A	9/1998	Schwartz	
5,800,508 A	9/1998	Goicoechea et al.	
5,807,861 A	9/1998	Klein et al.	
5,811,447 A	9/1998	Kunz et al.	
5,820,917 A	10/1998	Tuch	
5,820,918 A	10/1998	Ronan et al.	
5,824,048 A	10/1998	Tuch	
5,824,049 A	10/1998	Ragheb et al.	
5,833,651 A	11/1998	Donovan et al.	
5,837,008 A	11/1998	Berg et al.	
5,837,313 A	11/1998	Ding et al.	
5,843,172 A	12/1998	Yan	
5,849,034 A	12/1998	Schwartz	
5,851,217 A	12/1998	Wolff et al.	
5,851,231 A	12/1998	Wolff et al.	
5,858,990 A	1/1999	Walsh	
5,861,027 A	1/1999	Trapp	
5,865,814 A	2/1999	Tuch	
5,871,535 A	2/1999	Wolff et al.	
5,873,904 A	2/1999	Ragheb et al.	
5,876,433 A	3/1999	Lunn	
5,879,697 A	3/1999	Ding et al.	
5,882,335 A	3/1999	Leone et al.	
5,891,108 A	4/1999	Leone et al.	
5,900,246 A	5/1999	Lambert	
5,902,266 A	5/1999	Leone et al.	
5,912,253 A *	6/1999	Cottens et al.	514/291
5,932,580 A	8/1999	Levitzki et al.	
5,951,586 A	9/1999	Berg et al.	
5,957,971 A	9/1999	Schwartz	
5,972,027 A	10/1999	Johnson	
5,976,534 A	11/1999	Hart et al.	
5,977,163 A	11/1999	Li et al.	
5,980,553 A	11/1999	Gray et al.	
5,980,566 A	11/1999	Alt et al.	
5,980,972 A	11/1999	Ding	
5,981,568 A	11/1999	Kunz et al.	
5,985,307 A	11/1999	Hanson et al.	
5,997,468 A	12/1999	Wolff et al.	
6,004,346 A	12/1999	Wolff et al.	
6,039,721 A	3/2000	Johnson et al.	
6,059,813 A	5/2000	Vrba et al.	
6,071,305 A	6/2000	Brown et al.	
6,074,659 A	6/2000	Kunz et al.	
6,080,190 A	6/2000	Schwartz	
6,096,070 A	8/2000	Ragheb et al.	
6,120,536 A	9/2000	Dinge et al.	
6,136,798 A	10/2000	Cody et al.	
6,140,127 A	10/2000	Sprague	
6,146,358 A	11/2000	Rowe	
6,153,252 A	11/2000	Hossainy et al.	
6,171,232 B1	1/2001	Papandreou et al.	
6,171,609 B1	1/2001	Kunz	
6,177,272 B1	1/2001	Nabel et al.	
6,214,901 B1	4/2001	Chudzik et al.	
6,240,616 B1	6/2001	Yan	
6,254,632 B1	7/2001	Wu et al.	
6,258,121 B1	7/2001	Yang et al.	
6,268,390 B1	7/2001	Kunz	
6,273,913 B1	8/2001	Wright et al.	
6,287,320 B1	9/2001	Slepian	
6,287,628 B1	9/2001	Hossainy et al.	
6,306,421 B1	10/2001	Kunz et al.	
6,313,264 B1	11/2001	Caggiano et al.	
6,369,039 B1 *	4/2002	Palasis et al.	424/93.2
6,379,382 B1	4/2002	Yang	
6,517,858 B1	2/2003	Le Moal et al.	
6,585,764 B2	7/2003	Wright et al.	
2001/0007083 A1	7/2001	Roorda	
2002/0010418 A1	1/2002	Lary et al.	
2002/0061326 A1	5/2002	Li et al.	
2002/0082680 A1	6/2002	Shanley	
2002/0082685 A1	6/2002	Sirhan et al.	
2002/0095114 A1	7/2002	Palasis	
2002/0103505 A1	8/2002	Thompson	
2002/0103526 A1	8/2002	Steinke	
2002/0119178 A1	8/2002	Levesque et al.	
2002/0127327 A1	9/2002	Schwarz et al.	
2002/0133224 A1	9/2002	Bajgar et al.	
2002/0193475 A1	12/2002	Hossainy et al.	

FOREIGN PATENT DOCUMENTS

EP	604 022 A1	6/1994
EP	621 015 A1	10/1994
EP	623 354 A1	11/1994
EP	734698 A2	3/1996

EP	0 712 615	5/1996
EP	716 836 A1	6/1996
EP	0 716 836	6/1996
EP	800801 A1	8/1996
EP	734 721 A1	10/1996
EP	0 761 251	3/1997
EP	830853 A1	7/1997
EP	0 850 651	7/1998
EP	0 938 878 A2	9/1999
EP	0 938 878 A3	9/1999
EP	950 386 A2	10/1999
FR	0 566 807 A1	4/1992
GB	0 662 307 A2	12/1951
GB	1 205 743	9/1970
WO	WO 91/2779	9/1991
WO	WO 92/15286 A1	9/1992
WO	WO 94/01056 A1	1/1994
WO	WO 94/21308 A1	9/1994
WO	WO 94/21309 A1	9/1994
WO	WO 94/24961 A1	11/1994
WO	WO 96/00272 A1	1/1996
WO	WO 96/26689	9/1996
WO	WO 96/32907	10/1996
WO	WO 96/34580	11/1996
WO	WO 97/25000	7/1997
WO	WO 97/33534 A1	9/1997
WO	WO 98/13344 A1	4/1998
WO	WO 98/19628	5/1998
WO	WO 98/23228	6/1998
WO	WO 98/23244	6/1998
WO	WO 98/34669	8/1998
WO	WO 98/36784 A1	8/1998
WO	WO 98/47447 A1	10/1998
WO	WO 98/56312 A1	12/1998
WO	WO 00/21584	4/2000
WO	WO 00/27445 A1	5/2000
WO	WO 00/32255 A1	6/2000

* cited by examiner

FIG. 1

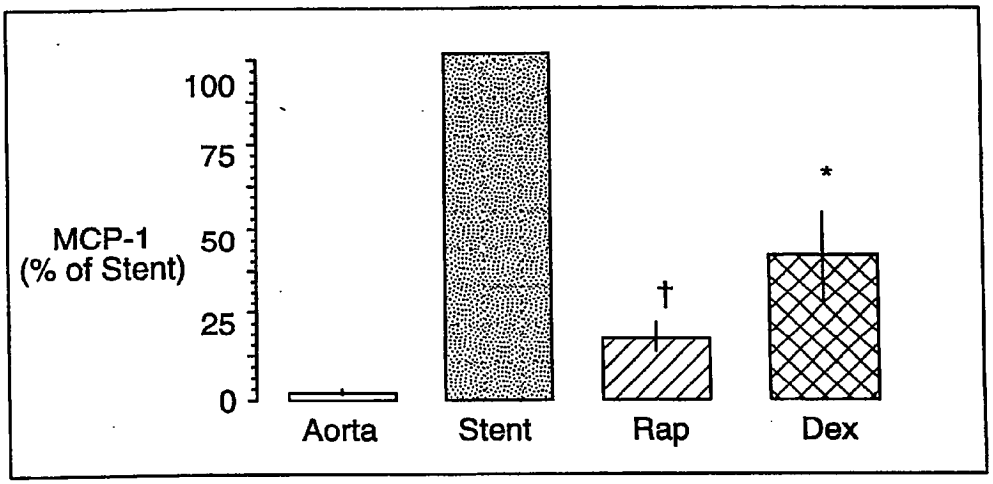


FIG. 2

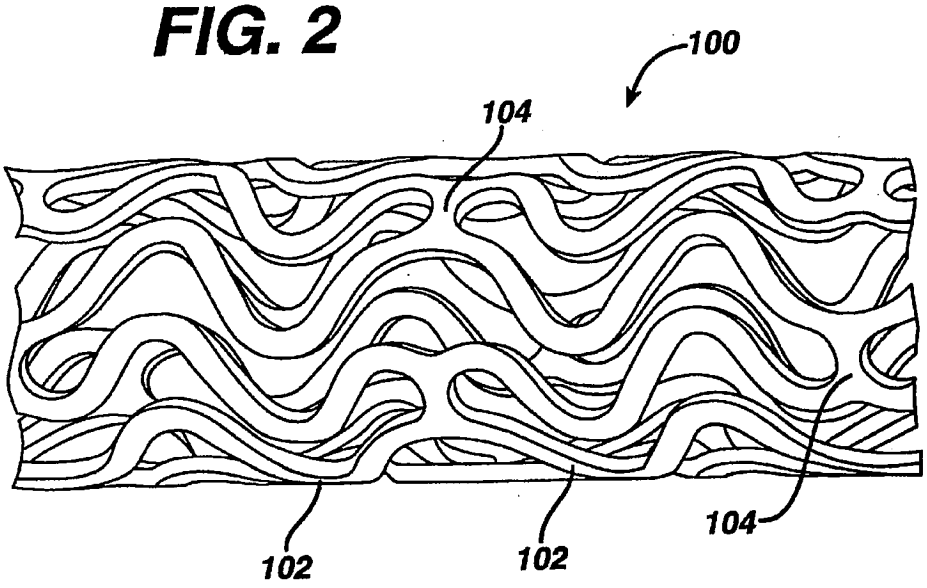
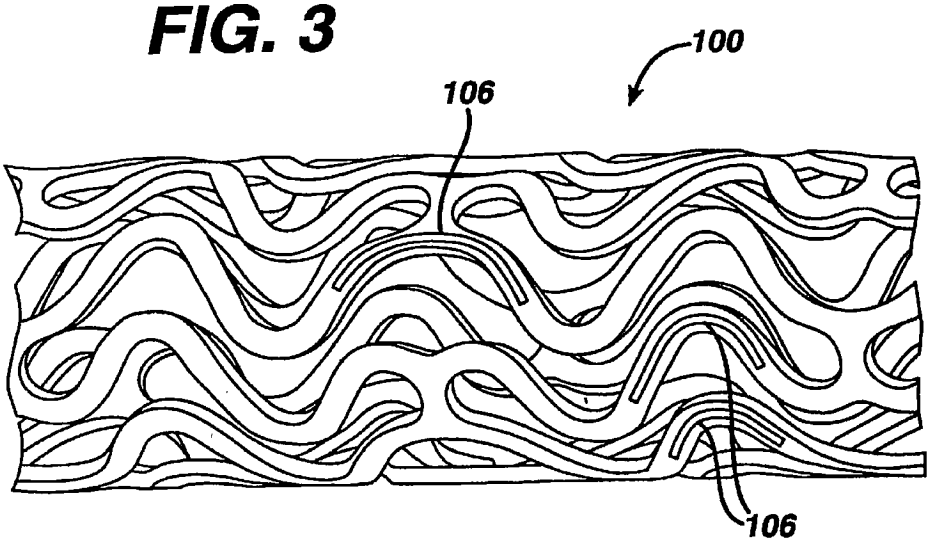


FIG. 3



ANTIINFLAMMATORY DRUG AND DELIVERY DEVICE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part application of U.S. application Ser. No. 09/575,480, filed on May 19, 2000 which claims the benefit of U.S. Provisional Application No. 60/204,417, filed May 12, 2000 and claims the benefit of, U.S. Provisional Application No. 60/262,614, filed Jan. 18, 2001, U.S. Provisional Application No. 60/262,461, filed Jan. 18, 2001, U.S. Provisional Application No. 60/263,806, filed Jan. 24, 2001 and U.S. Provisional Application No. 60/263,979, filed Jan. 25, 2001.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to drugs and drug delivery systems for the prevention and treatment of vascular disease, and more particularly to drugs and drug delivery systems for the prevention and treatment of neointimal hyperplasia.

2. Discussion of the Related Art

Many individuals suffer from circulatory disease caused by a progressive blockage of the blood vessels that perfuse the heart and other major organs with nutrients. More severe blockage of blood vessels in such individuals often leads to hypertension, ischemic injury, stroke, or myocardial infarction. Atherosclerotic lesions, which limit or obstruct coronary blood flow, are the major cause of ischemic heart disease. Percutaneous transluminal coronary angioplasty is a medical procedure whose purpose is to increase blood flow through an artery. Percutaneous transluminal coronary angioplasty is the predominant treatment for coronary vessel stenosis. The increasing use of this procedure is attributable to its relatively high success rate and its minimal invasiveness compared with coronary bypass surgery. A limitation associated with percutaneous transluminal coronary angioplasty is the abrupt closure of the vessel which may occur immediately after the procedure and restenosis which occurs gradually following the procedure. Additionally, restenosis is a chronic problem in patients who have undergone saphenous vein bypass grafting. The mechanism of acute occlusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets and fibrin along the damaged length of the newly opened blood vessel.

Restenosis after percutaneous transluminal coronary angioplasty is a more gradual process initiated by vascular injury. Multiple processes, including thrombosis, inflammation, growth factor and cytokine release, cell proliferation, cell migration and extracellular matrix synthesis each contribute to the restenotic process.

While the exact mechanism of restenosis is not completely understood, the general aspects of the restenosis process have been identified. In the normal arterial wall, smooth muscle cells proliferate at a low rate, approximately less than 0.1 percent per day. Smooth muscle cells in the vessel walls exist in a contractile phenotype characterized by eighty to ninety percent of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, Golgi, and free ribosomes are few and are located in the perinuclear region. Extracellular matrix surrounds the smooth muscle cells and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining smooth muscle cells in the contractile phenotypic state (Campbell and Campbell, 1985).

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the vessel wall become injured, initiating a thrombotic and inflammatory response. Cell derived growth factors such as platelet derived growth factor, fibroblast growth factor, epidermal growth factor, thrombin, etc., released from platelets, invading macrophages and/or leukocytes, or directly from the smooth muscle cells provoke proliferative and migratory responses in medial smooth muscle cells. These cells undergo a change from the contractile phenotype to a synthetic phenotype characterized by only a few contractile filament bundles, extensive rough endoplasmic reticulum, Golgi and free ribosomes. Proliferation/migration usually begins within one to two days post-injury and peaks several days thereafter (Campbell and Campbell, 1987; Clowes and Schwartz, 1985).

Daughter cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate and secrete significant amounts of extracellular matrix proteins. Proliferation, migration and extracellular matrix synthesis continue until the damaged endothelial layer is repaired at which time proliferation slows within the intima, usually within seven to fourteen days post-injury. The newly formed tissue is called neointima. The further vascular narrowing that occurs over the next three to six months is due primarily to negative or constrictive remodeling.

Simultaneous with local proliferation and migration, inflammatory cells invade the site of vascular injury. Within three to seven days post-injury, inflammatory cells have migrated to the deeper layers of the vessel wall. In animal models employing either balloon injury or stent implantation, inflammatory cells may persist at the site of vascular injury for at least thirty days (Tanaka et al., 1993; Edelman et al., 1998). Inflammatory cells therefore are present and may contribute to both the acute and chronic phases of restenosis.

Numerous agents have been examined for presumed anti-proliferative actions in restenosis and have shown some activity in experimental animal models. Some of the agents which have been shown to successfully reduce the extent of intimal hyperplasia in animal models include: heparin and heparin fragments (Clowes, A. W. and Karnovsky M., Nature 265: 25–26, 1977; Guyton, J. R. et al., Circ. Res., 46: 625–634, 1980; Clowes, A. W. and Clowes, M. M., Lab. Invest. 52: 611–616, 1985; Clowes, A. W. and Clowes, M. M., Circ. Res. 58: 839–845, 1986; Majesky et al., Circ. Res. 61: 296–300, 1987; Snow et al., Am. J. Pathol. 137: 313–330, 1990; Okada, T. et al., Neurosurgery 25: 92–98, 1989), colchicine (Currier, J. W. et al., Circ. 80: 11–66, 1989), taxol (Sollot, S. J. et al., J. Clin. Invest. 95: 1869–1876, 1995), angiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., Science, 245: 186–188, 1989), angiopeptin (Lundergan, C. F. et al. Am. J. Cardiol. 17(Suppl. B):132B-136B, 1991), cyclosporin A (Jonasson, L. et al., Proc. Natl., Acad. Sci., 85: 2303, 1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., Science 253: 1129–1132, 1991), terbinafine (Nemecek, G. M. et al., J. Pharmacol. Exp. Thera. 248: 1167–1174, 1989), trapidil (Liu, M. W. et al., Circ. 81: 1089–1093, 1990), tranilast (Fukuyama, J. et al., Eur. J. Pharmacol. 318: 327–332, 1996), interferon-gamma (Hansson, G. K. and Holm, J., Circ. 84:1266–1272, 1991), rapamycin (Marx, S. O. et al., Circ. Res. 76: 412417, 1995), corticosteroids (Colburn, M. D. et al., J. Vasc. Surg. 15: 510–518, 1992), see also Berk, B. C. et al., J. Am. Coll. Cardiol. 17: 111 B-117B, 1991), ionizing radiation (Weinberger, J. et al., Int. J. Rad. Onc. Biol. Phys. 36: 767–775, 1996), fusion toxins (Farb, A. et al.,

Circ. Res. 80: 542–550, 1997) antisense oligonucleotides (Simons, M. et al., Nature 359: 67–70, 1992) and gene vectors (Chang, M. W. et al., J. Clin. Invest. 96: 2260–2268, 1995). Anti-proliferative effects on smooth muscle cells in vitro have been demonstrated for many of these agents, including heparin and heparin conjugates, taxol, tranilast, colchicine, ACE inhibitors, fusion toxins, antisense oligonucleotides, rapamycin and ionizing radiation. Thus, agents with diverse mechanisms of smooth muscle cell inhibition may have therapeutic utility in reducing intimal hyperplasia.

However, in contrast to animal models, attempts in human angioplasty patients to prevent restenosis by systemic pharmacologic means have thus far been unsuccessful. Neither aspirin-dipyridamole, ticlopidine, anti-coagulant therapy (acute heparin, chronic warfarin, hirudin or hirulog), thromboxane receptor antagonism nor steroids have been effective in preventing restenosis, although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty (Mak and Topol, 1997; Lang et al., 1991; Popma et al., 1991). The platelet GP IIb/IIIa receptor, antagonist, Reopro is still under study but has not shown promising results for the reduction in restenosis following angioplasty and stenting. Other agents, which have also been unsuccessful in the prevention of restenosis, include the calcium channel antagonists, prostacyclin mimetics, angiotensin converting enzyme inhibitors, serotonin receptor antagonists, and anti-proliferative agents. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; anti-proliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Mak and Topol, 1997; Lang et al., 1991; Popma et al., 1991).

Additional clinical trials in which the effectiveness for preventing restenosis utilizing dietary fish oil supplements or cholesterol lowering agents has been examined showing either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Mak and Topol, 1997; Franklin and Faxon, 1993: Serruys, P. W. et al., 1993). Recent observations suggest that the antilipid/antioxidant agent, probucol may be useful in preventing restenosis but this work requires confirmation (Tardif et al., 1997; Yokoi, et al., 1997). Probucol is presently not approved for use in the United States and a thirty-day pretreatment period would preclude its use in emergency angioplasty. Additionally, the application of ionizing radiation has shown significant promise in reducing or preventing restenosis after angioplasty in patients with stents (Teirstein et al., 1997). Currently, however, the most effective treatments for restenosis are repeat angioplasty, atherectomy or coronary artery bypass grafting, because no therapeutic agents currently have Food and Drug Administration approval for use for the prevention of post-angioplasty restenosis.

Unlike systemic pharmacologic therapy, stents have proven effective in significantly reducing restenosis. Typically, stents are balloon-expandable slotted metal tubes (usually, but not limited to, stainless steel), which, when expanded within the lumen of an angioplastied coronary artery, provide structural support through rigid scaffolding to the arterial wall. This support is helpful in maintaining vessel lumen patency. In two randomized clinical trials, stents increased angiographic success after percutaneous transluminal coronary angioplasty, by increasing minimal lumen diameter and reducing, but not eliminating, the incidence of restenosis at six months (Serruys et al., 1994; Fischman et al., 1994).

Additionally, the heparin coating of stents appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 1996). Thus, sustained mechanical expansion of a stenosed coronary artery with a stent has been shown to provide some measure of restenosis prevention, and the coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs locally, at the site of injured tissue.

Accordingly, there exists a need for effective drugs and drug delivery systems for the effective prevention and treatment of neointimal thickening that occurs after percutaneous transluminal coronary angioplasty and stent implantation.

SUMMARY OF THE INVENTION

The drugs and drug delivery systems of the present invention provide a means for overcoming the difficulties associated with the methods and devices currently in use as briefly described above.

In accordance with one aspect, the present invention is directed to a method for the treatment of intimal hyperplasia in vessel walls. The method comprises the controlled delivery, by release from an intraluminal medical device, of an anti-inflammatory agent in therapeutic dosage amounts.

In accordance with another aspect, the present invention is directed to a drug delivery device. The drug delivery device comprises an intraluminal medical device and a therapeutic dosage of an agent releasably affixed to the intraluminal medical device for the treatment of inflammation caused by injury.

In accordance with another aspect, the present invention is directed to a method for the treatment of inflammation in vessel walls. The method comprises the controlled delivery, by release from an intraluminal medical device, of an anti-inflammatory agent in therapeutic dosage amounts.

The drugs and drug delivery systems of the present invention utilize a stent or graft in combination with rapamycin or other drugs/agents/compounds to prevent and treat neointimal hyperplasia, i.e. restenosis, following percutaneous transluminal coronary angioplasty and stent implantation. It has been determined that rapamycin functions to inhibit smooth muscle cell proliferation through a number of mechanisms. It has also been determined that rapamycin eluting stent coatings produce superior effects in humans, when compared to animals, with respect to the magnitude and duration of the reduction in neointimal hyperplasia. Rapamycin administration from a local delivery platform also produces an anti-inflammatory effect in the vessel wall that is distinct from and complimentary to its smooth muscle cell anti-proliferative effect. In addition, it has also been demonstrated that rapamycin inhibits constrictive vascular remodeling in humans.

Other drugs, agents or compounds which mimic certain actions of rapamycin may also be utilized in combination with local delivery systems or platforms.

The local administration of drugs, agents or compounds to stented vessels have the additional therapeutic benefit of higher tissue concentration than that which would be achievable through the systemic administration of the same drugs, agents or compounds. Other benefits include reduced systemic toxicity, single treatment, and ease of administration. An additional benefit of a local delivery device and drug,

agent or compound therapy may be to reduce the dose of the therapeutic drugs, agents or compounds and thus limit their toxicity, while still achieving a reduction in restenosis.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other features and advantages of the invention will be apparent from the following, more particular description of preferred embodiments of the invention, as illustrated in the accompanying drawings.

FIG. 1 is a chart indicating the effectiveness of rapamycin as an anti-inflammatory relative to other anti-inflammatories.

FIG. 2 is a view along the length of a stent (ends not shown) prior to expansion showing the exterior surface of the stent and the characteristic banding pattern.

FIG. 3 is a perspective view of the stent of FIG. 1 having reservoirs in accordance with the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As stated above, the proliferation of vascular smooth muscle cells in response to mitogenic stimuli that are released during balloon angioplasty and stent implantation is the primary cause of neointimal hyperplasia. Excessive neointimal hyperplasia can often lead to impairment of blood flow, cardiac ischemia and the need for a repeat intervention in selected patients in high risk treatment groups. Yet repeat revascularization incurs risk of patient morbidity and mortality while adding significantly to the cost of health care. Given the widespread use of stents in interventional practice, there is a clear need for safe and effective inhibitors of neointimal hyperplasia.

Rapamycin is a macroyclic triene antibiotic produced by streptomyces hygroscopicus as disclosed in U.S. Pat. No. 3,929,992. It has been found that rapamycin inhibits the proliferation of vascular smooth muscle cells in vivo. Accordingly, rapamycin may be utilized in treating intimal smooth muscle cell hyperplasia, restenosis and vascular occlusion in a mammal, particularly following either biologically or mechanically mediated vascular injury, or under conditions that would predispose a mammal to suffering such a vascular injury. Rapamycin functions to inhibit smooth muscle cell proliferation and does not interfere with the re-endothelialization of the vessel walls.

Rapamycin functions to inhibit smooth muscle cell proliferation through a number of mechanisms. In addition, rapamycin reduces the other effects caused by vascular injury, for example, inflammation. The operation and various functions of rapamycin are described in detail below. Rapamycin as used throughout this application shall include rapamycin, rapamycin analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

Rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during angioplasty. Inhibition of growth factor and cytokine mediated smooth muscle proliferation at the late G1 phase of the cell cycle is believed to be the dominant mechanism of action of rapamycin. However, rapamycin is also known to prevent T-cell proliferation and differentiation when administered systemically. This is the basis for its immunosuppresive activity and its ability to prevent graft rejection.

The molecular events that are responsible for the actions of rapamycin, a known anti-proliferative, which acts to reduce the magnitude and duration of neointimal hyperplasia, are still being elucidated. It is known, however, that rapamycin enters cells and binds to a high-affinity cytosolic protein called FKBP12. The complex of rapamycin and FKPB12 in turn binds to and inhibits a phosphoinositide (PI)-3 kinase called the "mammalian Target of Rapamycin" or TOR. TOR is a protein kinase that plays a key role in mediating the downstream signaling events associated with mitogenic growth factors and cytokines in smooth muscle cells and T lymphocytes. These events include phosphorylation of p27, phosphorylation of p70 s6 kinase and phosphorylation of 4BP-1, an important regulator of protein translation.

It is recognized that rapamycin reduces restenosis by inhibiting neointimal hyperplasia. However, there is evidence that rapamycin may also inhibit the other major component of restenosis, namely, negative remodeling. Remodeling is a process whose mechanism is not clearly understood but which results in shrinkage of the external elastic lamina and reduction in lumenal area over time, generally a period of approximately three to six months in humans.

Negative or constrictive vascular remodeling may be quantified angiographically as the percent diameter stenosis at the lesion site where there is no stent to obstruct the process. If late lumen loss is abolished in-lesion, it may be inferred that negative remodeling has been inhibited. Another method of determining the degree of remodeling involves measuring in-lesion external elastic lamina area using intravascular ultrasound (IVUS). Intravascular ultrasound is a technique that can image the external elastic lamina as well as the vascular lumen. Changes in the external elastic lamina proximal and distal to the stent from the post-procedural timepoint to four-month and twelve-month follow-ups are reflective of remodeling changes.

Evidence that rapamycin exerts an effect on remodeling comes from human implant studies with rapamycin coated stents showing a very low degree of restenosis in-lesion as well as in-stent. In-lesion parameters are usually measured approximately five millimeters on either side of the stent i.e. proximal and distal. Since the stent is not present to control remodeling in these zones which are still affected by balloon expansion, it may be inferred that rapamycin is preventing vascular remodeling.

The data in Table 1 below illustrate that in-lesion percent diameter stenosis remains low in the rapamycin treated groups, even at twelve months. Accordingly, these results support the hypothesis that rapamycin reduces remodeling.

TABLE 1.0

Angiographic In-Lesion Percent Diameter Stenosis (%, mean ± SD and "n=" In Patients Who Received a Rapamycin-Coated Stent

Coating Group	Post Placement	4–6 month Follow Up	12 month Follow Up
Brazil	10.6 ± 5.7 (30)	13.6 ± 8.6 (30)	22.3 ± 7.2 (15)
Netherlands	14.7 ± 8.8	22.4 ± 6.4	—

Additional evidence supporting a reduction in negative remodeling with rapamycin comes from intravascular ultrasound data that was obtained from a first-in-man clinical program as illustrated in Table 2 below.

TABLE 2.0

Matched IVUS data in Patients Who Received a Rapamycin-Coated Stent

IVUS Parameter	Post (n=)	4-Month Follow-Up (n=)	12-Month Follow-Up (n=)
Mean proximal vessel area (mm^2)	16.53 ± 3.53 (27)	16.31 ± 4.36 (28)	13.96 ± 2.26 (13)
Mean distal vessel area (mm^2)	13.12 ± 3.68 (26)	13.53 ± 4.17 (26)	12.49 ± 3.25 (14)

The data illustrated that there is minimal loss of vessel area proximally or distally which indicates that inhibition of negative remodeling has occurred in vessels treated with rapamycin-coated stents.

Other than the stent itself, there have been no effective solutions to the problem of vascular remodeling. Accordingly, rapamycin may represent a biological approach to controlling the vascular remodeling phenomenon.

It may be hypothesized that rapamycin acts to reduce negative remodeling in several ways. By specifically blocking the proliferation of fibroblasts in the vascular wall in response to injury, rapamycin may reduce the formation of vascular scar tissue. Rapamycin may also affect the translation of key proteins involved in collagen formation or metabolism.

Rapamycin used in this context includes rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

In a preferred embodiment, the rapamycin is delivered by a local delivery device to control negative remodeling of an arterial segment after balloon angioplasty as a means of reducing or preventing restenosis. While any delivery device may be utilized, it is preferred that the delivery device comprises a stent that includes a coating or sheath which elutes or releases rapamycin. The delivery system for such a device may comprise a local infusion catheter that delivers rapamycin at a rate controlled by the administrator.

Rapamycin may also be delivered systemically using an oral dosage form or a chronic injectible depot form or a patch to deliver rapamycin for a period ranging from about seven to forty-five days to achieve vascular tissue levels that are sufficient to inhibit negative remodeling. Such treatment is to be used to reduce or prevent restenosis when administered several days prior to elective angioplasty with or without a stent.

Data generated in porcine and rabbit models show that the release of rapamycin into the vascular wall from a nonerodible polymeric stent coating in a range of doses (35–430 ug/15–18 mm coronary stent) produces a peak fifty to fifty-five percent reduction in neointimal hyperplasia as set forth in Table 3 below. This reduction, which is maximal at about twenty-eight to thirty days, is typically not sustained in the range of ninety to one hundred eighty days in the porcine model as set forth in Table 4 below.

TABLE 3.0

Animal Studies with Rapamycin-coated stents.
Values are mean ± Standard Error of Mean

Study	Duration	Stent[1]	Rapamycin	N	Neointimal Area (mm^2)	% Change From Polyme	% Change From Metal
Porcine							
98009	14 days	Metal		8	2.04 ± 0 17		
		1X + rapamycin	153 μg	8	1.66 ± 0.17*	–42%	–19%
		1X + TC300 + rapamycin	155 μg	8	1.51 ± 0.19*	–47%	–26%
99005	28 days	Metal		10	2.29 ± 0.21		
				9	3.91 ± 0.60**		
		1X + TC30 + rapamycin	130 μg	8	2.81 ± 0.34		+23%
		1X + TC100 + rapamycin	120 μg	9	2.62 ± 0.21		+14%
99006	28 days	Metal		12	4.57 ± 0.46		
		EVA/BMA 3X		12	5.02 ± 0.62		+10%
		1X + rapamycin	125 μg	11	2.84 ± 0.31* **	–43%	–38%
		3X + rapamycin	430 μg	12	3.06 ± 0.17* **	–39%	–33%
		3X + rapamycin	157 μg	12	2.77 ± 0.41* **	–45%	–39%
99011	28 days	Metal		11	3.09 ± 0.27		
				11	4.52 ± 0.37		
		1X + rapamycin	189 μg	14	3.05 ± 0.35		–1%
		3X + rapamycin/dex	182/363 μg	14	2.72 ± 0.71		–12%
99021	60 days	Metal		12	2.14 ± 0.25		
		1X + rapamycin	181 μg	12	2.95 ± 0.38		+38%
99034	28 days	Metal		8	5.24 ± 0.58		
		1X + rapamycin	186 μg	8	2.47 ± 0.33**		–53%
		3X + rapamycin/dex	185/369 μg	6	2.42 ± 0.64**		–54%
20001	28 days	Metal		6	1.81 ± 0.09		
		1X + rapamycin	172 μg	5	1.66 ± 0.44		–8%
20007							
	30 days	Metal		9	2.94 ± 0.43		
		1XTC + rapamycin	155 μg	10	1.40 ± 0.11*		–52%*

TABLE 3.0-continued

Animal Studies with Rapamycin-coated stents.
Values are mean ± Standard Error of Mean

Study	Duration	Stent[1]	Rapamycin	N	Neointimal Area (mm^2)	% Change From Polyme	% Change From Metal
Rabbit							
99019	28 days	Metal		8	1.20 ± 0.07		
		EVA/BMA 1X		10	1.26 ± 0.16		+5%
		1X + rapamycin	64 μg	9	0.92 ± 0.14	−27%	−23%
		1X + rapamycin	196 μg	10	0.66 ± 0.12* **	−48%	−45%
99020	28 days	Metal		12	1.18 ± 0.10		
		EVA/BMA 1X + rapamycin	197 μg	8	0.81 ± 0.16		−32%

[1]Stent nomenclature: EVA/BMA 1X, 2X, and 3X signifies approx. 500 μg, 1000 μg, and 1500 μg total mass (polymer + drug), respectively.
TC, top coat of 30 μg, 100 μg, or 300 μg drug-free BMA;
Biphasic; 2x 1X layers of rapamycin in EVA/BMA spearated by a 100 μg drug-free BMA layer.
[2]0.25 mg/kg/d × 14 d preceeded by a loading dose of 0.5 mg/kg/d × 3d prior to stent implantation.
*p < 0 05 from EVA/BMA control.
**p < 0.05 from Metal;
#Inflammation score: (0 = essentially no intimal involvement;
1 = <25% intima involved;
2 = ≧25% intima involved;
3 = >50% intima involved).

TABLE 4.0

180 day Porcine Study with Rapamycin-coated stents.
Values are mean ± Standard Error of Mean

Study	Duration	Stent[1]	Rapamycin	N	Neointimal Area (mm^2)	% Change From Polyme	% Change From Metal	Inflammation Score #
20007	3 days	Metal		10	0.38 ± 0.06			1.05 ± 0.06
(ETP-2-002233-P)		1XTC + rapamycin	155 μg	10	0.29 ± 0 03		−24%	1.08 ± 0.04
	30 days	Metal		9	2.94 ± 0.43			0.11 ± 0.08
		1XTC + rapamycin	155 μg	10	1.40 ± 0.11*		−52%*	0.25 ± 0.10
	90 days	Metal		10	3.45 ± 0.34			0.20 ± 0.08
		1XTC + rapamycin	155 μg	10	3.03 ± 0.29		−12%	0.80 ± 0.23
		1X + rapamycin	171 μg	10	2.86 ± 0.35		−17%	0.60 ± 0.23
	180 days	Metal		10	3.65 ± 0.39			0.65 ± 0.21
		1XTC + rapamycin	155 μg	10	3.34 ± 0.31		−8%	1.50 ± 0.34
		1X + rapamycin	171 μg	10	3.87 ± 0.28		+6%	1.68 ± 0.37

The release of rapamycin into the vascular wall of a human from a nonerodible polymeric stent coating provides superior results with respect to the magnitude and duration of the reduction in neointimal hyperplasia within the stent as compared to the vascular walls of animals as set forth above.

Humans implanted with a rapamycin coated stent comprising rapamycin in the same dose range as studied in animal models using the same polymeric matrix, as described above, reveal a much more profound reduction in neointimal hyperplasia than observed in animal models, based on the magnitude and duration of reduction in neointima. The human clinical response to rapamycin reveals essentially total abolition of neointimal hyperplasia inside the stent using both angiographic and intravascular ultrasound measurements. These results are sustained for at least one year as set forth in Table 5 below.

TABLE 5.0

Patients Treated (N = 45 patients) with a Rapamycin-coated Stent

Effectiveness Measures	Sirolimus FIM (N = 45 Patients, 45 Lesions)	95% Confidence Limit
Procedure Success (QCA)	100.0% (45/45)	[92.1%, 100.0%]
4-month In-Stent Diameter Stenosis (%)		
Mean ± SD (N)	4.8% ± 6.1% (30)	[2.6%, 7.0%]
Range (min, max)	(−8.2%, 14.9%)	
6-month In-Stent Diameter Stenosis (%)		
Mean ± SD (N)	8.9% ± 7.6% (13)	[4.8%, 13.0%]
Range (min, max)	(−2.9%, 20.4%)	
12-month In-Stent		

TABLE 5.0-continued

Patients Treated (N = 45 patients) with a Rapamycin-coated Stent

Effectiveness Measures	Sirolimus FIM (N = 45 Patients, 45 Lesions)	95% Confidence Limit
Diameter Stenosis (%)		
Mean ± SD (N)	8.9% ± 6.1% (15)	[5.8%, 12.0%]
Range (min, max)	(−3.0%, 22.0%)	
4-month In-Stent Late Loss (mm)		
Mean ± SD (N)	0.00 ± 0.29 (30)	[−0.10, 0.10]
Range (min, max)	(−0.51, 0.45)	
6-month In-Stent Late Loss (mm)		
Mean ± SD (N)	0.25 ± 0.27 (13)	[0.10, 0.39]
Range (min, max)	(−0.51, 0.91)	
12-month In-Stent Late Loss (mm)		
Mean ± SD (N)	0.11 ± 0.36 (15)	[−0.08, 0.29]
Range (min, max)	(−0.51, 0.82)	
4-month Obstruction Volume (%) (IVUS)		
Mean ± SD (N)	10.48% ± 2.78% (28)	[9.45%, 11.51%]
Range (min, max)	(4.60%, 16.35%)	
6-month Obstruction Volume (%) (IVUS)		
Mean ± SD (N)	7.22% ± 4.60% (13)	[4.72%, 9.72%],
Range (min, max)	(3.82%, 19.88%)	
12-month Obstruction Volume (%) (IVUS)		
Mean ± SD (N)	2.11% ± 5.28% (15)	[0.00%, 4.78%],
Range (min, max)	(0.00%, 19.89%)	
6-month Target Lesion Revascularization (TLR)	0.0% (0/30)	[0.0%, 9.5%]
12-month Target Lesion Revascularization (TLR)	0.0% (0/15)	[0.0%, 18.1%]

QCA = Quantitative Coronary Angiography
SD = Standard Deviation
IVUS = Intravascular Ultrasound

Rapamycin produces an unexpected benefit in humans when delivered from a stent by causing a profound reduction in in-stent neointimal hyperplasia that is sustained for at least one year. The magnitude and duration of this benefit in humans is not predicted from animal model data. Rapamycin used in this context includes rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

These results may be due to a number of factors. For example, the greater effectiveness of rapamycin in humans is due to greater sensitivity of its mechanism(s) of action toward the pathophysiology of human vascular lesions compared to the pathophysiology of animal models of angioplasty. In addition, the combination of the dose applied to the stent and the polymer coating that controls the release of the drug is important in the effectiveness of the drug.

As stated above, rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during angioplasty injury. Also, it is known that rapamycin prevents T-cell proliferation and differentiation when administered systemically. It has also been determined that rapamycin exerts a local inflammatory effect in the vessel wall when administered from a stent in low doses for a sustained period of time (approximately two to six weeks). The local anti-inflammatory benefit is profound and unexpected. In combination with the smooth muscle anti-proliferative effect, this dual mode of action of rapamycin may be responsible for its exceptional efficacy.

Accordingly, rapamycin delivered from a local device platform, reduces neointimal hyperplasia by a combination of anti-inflammatory and smooth muscle anti-proliferative effects. Rapamycin used in this context means rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin. Local device platforms include stent coatings, stent sheaths, grafts and local drug infusion catheters or porous balloons or any other suitable means for the in situ or local delivery of drugs, agents or compounds.

The anti-inflammatory effect of rapamycin is evident in data from an experiment, illustrated in Table 6, in which rapamycin delivered from a stent was compared with dexamethasone delivered from a stent. Dexamethasone, a potent steroidal anti-inflammatory agent, was used as a reference standard. Although dexamethasone is able to reduce inflammation scores, rapamycin is far more effective than dexamethasone in reducing inflammation scores. In addition, rapamycin significantly reduces neointimal hyperplasia, unlike dexamethasone.

TABLE 6.0

Group Rapamycin Rap	N=	Neointimal Area (mm^2)	% Area Stenosis	Inflammation Score
Uncoated	8	5.24 ± 1.65	54 ± 19	0.97 ± 1.00
Dexmethasone (Dex)	8	4.31 ± 3.02	45 ± 31	0.39 ± 0.24
Rapamycin	7	2.47 ± 0.94*	26 ± 10*	0.13 ± 0.19*
Rap + Dex	6	2.42 ± 1.58*	26 ± 18*	0.17 ± 0.30*

*significance level P < 0.05

Rapamycin has also been found to reduce cytokine levels in vascular tissue when delivered from a stent. The data in FIG. 1 illustrates that rapamycin is highly effective in reducing monocyte chemotactic protein (MCP-1) levels in the vascular wall. MCP-1 is an example of a proinflammatory/chemotactic cytokine that is elaborated during vessel injury. Reduction in MCP-1 illustrates the beneficial effect of rapamycin in reducing the expression of proinflammatory mediators and contributing to the anti-inflammatory effect of rapamycin delivered locally from a stent. It is recognized that vascular inflammation in response to injury is a major contributor to the development of neointimal hyperplasia.

Since rapamycin may be shown to inhibit local inflammatory events in the vessel it is believed that this could explain the unexpected superiority of rapamycin in inhibiting neointima.

As set forth above, rapamycin functions on a number of levels to produce such desired effects as the prevention of T-cell proliferation, the inhibition of negative remodeling, the reduction of inflammation, and the prevention of smooth muscle cell proliferation. While the exact mechanisms of these functions are not completely known, the mechanisms that have been identified may be expanded upon.

Studies with rapamycin suggest that the prevention of smooth muscle cell proliferation by blockade of the cell cycle is a valid strategy for reducing neointimal hyperplasia. Dramatic and sustained reductions in late lumen loss and neointimal plaque volume have been observed in patients

receiving rapamycin delivered locally from a stent. The present invention expands upon the mechanism of rapamycin to include additional approaches to inhibit the cell cycle and reduce neointimal hyperplasia without producing toxicity.

The cell cycle is a tightly controlled biochemical cascade of events that regulate the process of cell replication. When cells are stimulated by appropriate growth factors, they move from G_0 (quiescence) to the G1 phase of the cell cycle. Selective inhibition of the cell cycle in the G1 phase, prior to DNA replication (S phase), may offer therapeutic advantages of cell preservation and viability while retaining anti-proliferative efficacy when compared to therapeutics that act later in the cell cycle i.e. at S, G2 or M phase.

Accordingly, the prevention of intimal hyperplasia in blood vessels and other conduit vessels in the body may be achieved using cell cycle inhibitors that act selectively at the G1 phase of the cell cycle. These inhibitors of the G1 phase of the cell cycle may be small molecules, peptides, proteins, oligonucleotides or DNA sequences. More specifically, these drugs or agents include inhibitors of cyclin dependent kinases (cdk's) involved with the progression of the cell cycle through the G1 phase, in particular cdk2 and cdk4.

Examples of drugs, agents or compounds that act selectively at the G1 phase of the cell cycle include small molecules such as flavopiridol and its structural analogs that have been found to inhibit cell cycle in the late G1 phase by antagonism of cyclin dependent kinases. Therapeutic agents that elevate an endogenous kinase inhibitory protein^{kip} called P27, sometimes referred to as P27^{kip1}, that selectively inhibits cyclin dependent kinases may be utilized. This includes small molecules, peptides and proteins that either block the degradation of P27 or enhance the cellular production of P27, including gene vectors that can transfact the gene to produce P27. Staurosporin and related small molecules that block the cell cycle by inhibiting protein kinases may be utilized. Protein kinase inhibitors, including the class of tyrphostins that selectively inhibit protein kinases to antagonize signal transduction in smooth muscle in response to a broad range of growth factors such as PDGF and FGF may also be utilized.

Any of the drugs, agents or compounds discussed above may be administered either systemically, for example, orally, intravenously, intramuscularly, subcutaneously, nasally or intradermally, or locally, for example, stent coating, stent covering or local delivery catheter. In addition, the drugs or agents discussed above may be formulated for fast-release or slow release with the objective of maintaining the drugs or agents in contact with target tissues for a period ranging from three days to eight weeks.

As set forth above, the complex of rapamycin and FKPB12 binds to and inhibits a phosphoinositide (PI)-3 kinase called the mammalian Target of Rapamycin or TOR. An antagonist of the catalytic activity of TOR, functioning as either an active site inhibitor or as an allosteric modulator, i.e. an indirect inhibitor that allosterically modulates, would mimic the actions of rapamycin but bypass the requirement for FKBP12. The potential advantages of a direct inhibitor of TOR include better tissue penetration and better physical/chemical stability. In addition, other potential advantages include greater selectivity and specificity of action due to the specificity of an antagonist for one of multiple isoforms of TOR that may exist in different tissues, and a potentially different spectrum of downstream effects leading to greater drug efficacy and/or safety.

The inhibitor may be a small organic molecule (approximate mw<1000), which is either a synthetic or naturally derived product. Wortmanin may be an agent which inhibits the function of this class of proteins. It may also be a peptide or an oligonucleotide sequence. The inhibitor may be administered either sytemically (orally, intravenously, intramuscularly, subcutaneously, nasally, or intradermally) or locally (stent coating, stent covering, local drug delivery catheter). For example, the inhibitor may be released into the vascular wall of a human from a nonerodible polymeric stent coating. In addition, the inhibitor may be formulated for fast-release or slow release with the objective of maintaining the rapamycin or other drug, agent or compound in contact with target tissues for a period ranging from three days to eight weeks.

As stated previously, the implantation of a coronary stent in conjunction with balloon angioplasty is highly effective in treating acute vessel closure and may reduce the risk of restenosis. Intravascular ultrasound studies (Mintz et al., 1996) suggest that coronary stenting effectively prevents vessel constriction and that most of the late luminal loss after stent implantation is due to plaque growth, probably related to neointimal hyperplasia. The late luminal loss after coronary stenting is almost two times higher than that observed after conventional balloon angioplasty. Thus, inasmuch as stents prevent at least a portion of the restenosis process, the use of drugs, agents or compounds which prevent inflammation and proliferation, or prevent proliferation by multiple mechanisms, combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

The local delivery of drugs, agents or compounds from a stent has the following advantages; namely, the prevention of vessel recoil and remodeling through the scaffolding action of the stent and the drugs, agents or compounds and the prevention of multiple components of neointimal hyperplasia. This local administration of drugs, agents or compounds to stented coronary arteries may also have additional therapeutic benefit. For example, higher tissue concentrations would be achievable than that which would occur with systemic administration, reduced systemic toxicity, and single treatment and ease of administration. An additional benefit of drug therapy may be to reduce the dose of the therapeutic compounds, thereby limiting their toxicity, while still achieving a reduction in restenosis.

There are a multiplicity of different stents that may be utilized following percutaneous transluminal coronary angioplasty. Although any number of stents may be utilized in accordance with the present invention, for simplicity, one particular stent will be described in exemplary embodiments of the present invention. The skilled artisan will recognize that any number of stents may be utilized in connection with the present invention.

A stent is commonly used as a tubular structure left inside the lumen of a duct to relieve an obstruction. Commonly, stents are inserted into the lumen in a non-expanded form and are then expanded autonomously, or with the aid of a second device in situ. A typical method of expansion occurs through the use of a catheter-mounted angioplasty balloon which is inflated within the stenosed vessel or body passageway in order to shear and disrupt the obstructions associated with the wall components of the vessel and to obtain an enlarged lumen. As set forth below, self-expanding stents may also be utilized.

FIG. **2** illustrates an exemplary stent **100** which may be utilized in accordance with an exemplary embodiment of the present invention. The expandable cylindrical stent **100** comprises a fenestrated structure for placement in a blood vessel, duct or lumen to hold the vessel, duct or lumen open,

more particularly for protecting a segment of artery from restenosis after angioplasty. The stent **100** may be expanded circumferentially and maintained in an expanded configuration, that is circumferentially or radially rigid. The stent **100** is axially flexible and when flexed at a band, the stent **100** avoids any externally-protruding component parts.

The stent **100** generally comprises first and second ends with an intermediate section therebetween. The stent **100** has a longitudinal axis and comprises a plurality of longitudinally disposed bands **102**, wherein each band **102** defines a generally continuous wave along a line segment parallel to the longitudinal axis. A plurality of circumferentially arranged links **104** maintain the bands **102** in a substantially tubular structure. Essentially, each longitudinally disposed band **102** is connected at a plurality of periodic locations, by a short circumferentially arranged link **104** to an adjacent band **102**. The wave associated with each of the bands **102** has approximately the same fundamental spatial frequency in the intermediate section, and the bands **102** are so disposed that the wave associated with them are generally aligned so as to be generally in phase with one another. As illustrated in the figure, each longitudinally arranged band **102** undulates through approximately two cycles before there is a link to an adjacent band.

The stent **100** may be fabricated utilizing any number of methods. For example, the stent **100** may be fabricated from a hollow or formed stainless steel tube that may be machined using lasers, electric discharge milling, chemical etching or other means. The stent **100** is inserted into the body and placed at the desired site in an unexpanded form. In one embodiment, expansion may be effected in a blood vessel by a balloon catheter, where the final diameter of the stent **100** is a function of the diameter of the balloon catheter used.

It should be appreciated that a stent **100** in accordance with the present invention may be embodied in a shape-memory material, including, for example, an appropriate alloy of nickel and titanium. In this embodiment, after the stent **100** has been formed it may be compressed so as to occupy a space sufficiently small as to permit its insertion in a blood vessel or other tissue by insertion means, wherein the insertion means include a suitable catheter, or flexible rod. On emerging from the catheter, the stent **100** may be configured to expand into the desired configuration where the expansion is automatic or triggered by a change in pressure, temperature or electrical stimulation.

FIG. **3** illustrates an exemplary embodiment of the present invention utilizing the stent **100** illustrated in FIG. **2**. As illustrated, the stent **100** may be modified to comprise a reservoir **106**. Each of the reservoirs may be opened or closed as desired. These reservoirs **106** may be specifically designed to hold the drug, agent, compound or combinations thereof to be delivered. Regardless of the design of the stent **100**, it is preferable to have the drug, agent, compound or combinations thereof dosage applied with enough specificity and a sufficient concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the bands **102** is preferably sized to adequately apply the drug/drug combination dosage at the desired location and in the desired amount.

In an alternate exemplary embodiment, the entire inner and outer surface of the stent **100** may be coated with various drug and drug combinations in therapeutic dosage amounts. A detailed description of exemplary coating techniques is described below.

Rapamycin or any of the drugs, agents or compounds described above may be incorporated into or affixed to the stent in a number of ways and utilizing any number of biocompatible materials. In the exemplary embodiment, the rapamycin is directly incorporated into a polymeric matrix and sprayed onto the outer surface of the stent. The rapamycin elutes from the polymeric matrix over time and enters the surrounding tissue. The rapamycin preferably remains on the stent for at least three days up to approximately six months and more preferably between seven and thirty days.

Any number of non-erodible polymers may be utilized in conjunction with rapamycin. In the exemplary embodiment, the polymeric matrix comprises two layers. The base layer comprises a solution of ethylene-co-vinylacetate and polybutylmethacrylate. The rapamycin is incorporated into this layer. The outer layer comprises only polybutylmethacrylate and acts as a diffusion barrier to prevent the rapamycin from eluting too quickly and entering the surrounding tissues. The thickness of the outer layer or top coat determines the rate at which the rapamycin elutes from the matrix. Essentially, the rapamycin elutes from the matrix by diffusion through the polymer molecules. Polymers are permeable, thereby allowing solids, liquids and gases to escape therefrom. The total thickness of the polymeric matrix is in the range from about 1 micron to about 20 microns or greater.

The ethylene-co-vinylacetate, polybutylmethacrylate and rapamycin solution may be incorporated into or onto the stent in a number of ways. For example, the solution may be sprayed onto the stent or the stent may be dipped into the solution. In a preferred embodiment, the solution is sprayed onto the stent and then allowed to dry. In another exemplary embodiment, the solution may be electrically charged to one polarity and the stent electrically changed to the opposite polarity. In this manner, the solution and stent will be attracted to one another. In using this type of spraying process, waste may be reduced and more control over the thickness of the coat may be achieved.

Since rapamycin works by entering the surrounding tissue, it is preferably only affixed to the surface of the stent making contact with one tissue. Typically, only the outer surface of the stent makes contact with the tissue. Accordingly, in a preferred embodiment, only the outer surface of the stent is coated with rapamycin. For other drugs, agents or compounds, the entire stent may be coated.

It is important to note that different polymers may be utilized for different stents. For example, in the above-described embodiment, ethylene-co-vinylacetate and polybutylmethacrylate are utilized to form the polymeric matrix. This matrix works well with stainless steel stents. Other polymers may be utilized more effectively with stents formed from other materials, including materials that exhibit superelastic properties such as alloys of nickel and titanium.

Although shown and described is what is believed to be the most practical and preferred embodiments, it is apparent that departures from specific designs and methods described and shown will suggest themselves to those skilled in the art and may be used without departing from the spirit and scope of the invention. The present invention is not restricted to the particular constructions described and illustrated, but should be constructed to cohere with all modifications that may fall within the scope of the appended claims.

What is claimed is:

1. A method for the treatment of intimal hyperplasia in vessel walls comprising the controlled delivery, by release, for a sustained period of time in the range from about two to about six weeks, from an implantable intraluminal medical device, of an anti-inflammatory agent in therapeutic dosage amounts, the anti-inflammatory agent comprises

analogs and congeners that bind a high affinity cytosolic protein, FKBP 12 and possesses the same pharmacologic properties as rapamycin.

2. Method for the treatment of intimal hyperplasia in vessel walls according to claim **1**, wherein the anti-inflammatory agent reduces inflammatory cytokine levels in vascular tissues.

3. The method for the treatment of intimal hyperplasia in vessel walls according to claim **1**, wherein the anti-inflammatory agent reduces monocyte chemotactic protein levels in vascular tissues.

4. The method for treatment of intimal hyperplasia in vessel walls according to claim **1**, wherein the anti-inflammatory agent comprises rapamycin.

5. A drug delivery device comprising:

an implantable intraluminal medical device; and

a therapeutic dosage of an agent releasably affixed to the implantable intraluminal medical device for the treatment of inflammation caused by injury, the agent being released for a sustained period of time in the range from about two to about six weeks, the anti-inflammatory agent comprises analogs and congeners that bind a high affinity cytosolic protein, FKBP 12 and posses the same pharmacologic properties as rapamycin.

6. The drug delivery device according to claim **5**, wherein the agent reduces inflammatory cytokine levels in vascular tissue.

7. The drug delivery device according to claim **5**, wherein the agent reduces monocyte chemotactic protein levels in vascular tissues.

8. The drug delivery device according to claim **5**, wherein the agent comprises rapamycin.

9. The drug delivery device according to claim **5**, wherein the intraluminal medical device comprises a stent.

10. The drug delivery device according to claim **9**, wherein the agent is incorporated in a non-erodible polymeric matrix coating affixed to the stent.

11. A method for the treatment of inflammation in vessel walls comprising the controlled delivery, by release, for a sustained period of time in the range from about two to about six weeks, from an implantable intraluminal medical device of an anti-inflammatory agent in therapeutic dosage amounts, the anti-inflammatory agent comprises analogs and congeners that bind a high affinity cytosolic protein, FKBP 12 and posses the same pharmacologic properties as rapamycin.

* * * * *

Exhibit D

US007217286B2

(12) **United States Patent**
Falotico et al.

(10) **Patent No.: US 7,217,286 B2**
(45) **Date of Patent: *May 15, 2007**

(54) **LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT**

(75) Inventors: **Robert Falotico**, Bell Mead, NJ (US); **Gerard H. Llanos**, Stewartsville, NJ (US)

(73) Assignee: **Cordis Corporation**, Miami Lakes, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/467,035**

(22) Filed: **Aug. 24, 2006**

(65) **Prior Publication Data**

US 2007/0021825 A1 Jan. 25, 2007

Related U.S. Application Data

(63) Continuation of application No. 10/951,385, filed on Sep. 28, 2004, which is a continuation of application No. 10/408,328, filed on Apr. 7, 2003, now Pat. No. 6,808,536, which is a continuation of application No. 09/874,117, filed on Jun. 4, 2001, now Pat. No. 6,585,764, which is a continuation of application No. 09/061,568, filed on Apr. 16, 1998, now Pat. No. 6,273,913.

(60) Provisional application No. 60/044,692, filed on Apr. 18, 1997.

(51) **Int. Cl.**
A61F 2/06 (2006.01)

(52) **U.S. Cl.** **623/1.42**

(58) **Field of Classification Search** 623/1.45–1.48; 427/2.1–2.31
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

861,659	A	7/1907	Johnston	464/147
3,051,677	A	8/1962	Rexford	522/156
3,279,996	A	10/1966	Long et al.	424/424
3,526,005	A	9/1970	Bokros	623/11.11
3,599,641	A	8/1971	Sheridan	604/256
3,657,744	A	4/1972	Ersek	128/898
3,744,596	A	7/1973	Sander	188/203
3,779,805	A	12/1973	Alsberg	427/105

(Continued)

FOREIGN PATENT DOCUMENTS

DE 3205942 A1 9/1983

(Continued)

OTHER PUBLICATIONS

U.S. Appl. No. 07/819,314, filed Jan. 9, 1992, Morris.

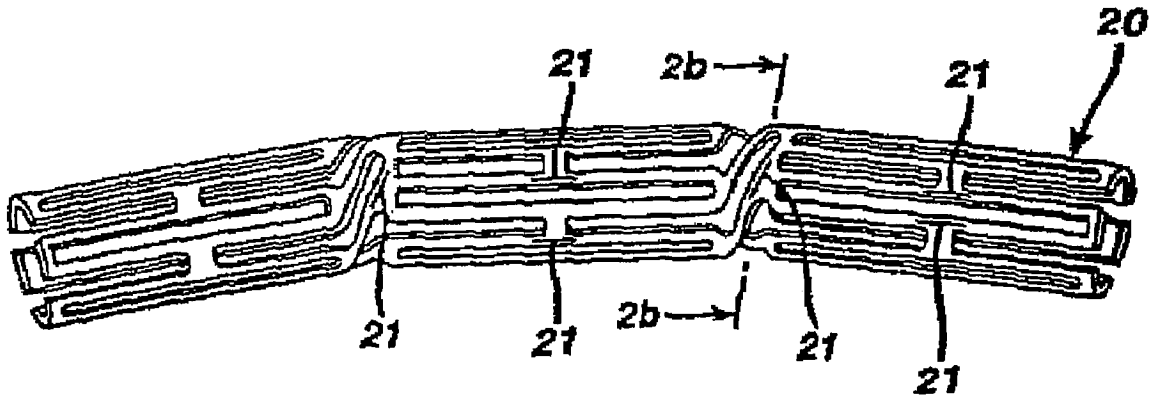
(Continued)

Primary Examiner—Suzette Gherbi
(74) *Attorney, Agent, or Firm*—Woodcock Washburn LLP

(57) **ABSTRACT**

Methods of preparing intravascular stents with a polymeric coating containing macrocyclic lactone (such as rapamycin or its analogs), stents and stent graphs with such coatings, and methods of treating a coronary artery with such devices. The macrocyclic lactone-based polymeric coating facilitates the performance of such devices in inhibiting restenosis.

5 Claims, 2 Drawing Sheets



U.S. PATENT DOCUMENTS

3,929,992	A	12/1975	Sehgal et al.	424/122
3,932,627	A	1/1976	Margraf	514/56
3,948,254	A	4/1976	Zaffaroni	128/833
3,952,334	A	4/1976	Bokros et al.	623/11.11
3,968,800	A	7/1976	Vilasi	606/198
4,069,307	A	1/1978	Higuchi et al.	424/432
4,076,285	A	2/1978	Martinez	285/332
4,292,965	A	10/1981	Nash et al.	128/833
4,299,226	A	11/1981	Banka	604/509
4,300,244	A	11/1981	Bokros	623/1.13
4,312,920	A	1/1982	Pierce et al.	428/425.5
4,321,711	A	3/1982	Mano	623/1.43
4,323,071	A	4/1982	Simpson et al.	606/194
4,390,599	A	6/1983	Broyles	428/597
4,413,359	A	11/1983	Akiyama et al.	623/23.72
4,423,183	A	12/1983	Close	524/546
4,441,216	A	4/1984	Ionescu et al.	623/2.19
4,503,569	A	3/1985	Dotter	623/1.19
4,512,338	A	4/1985	Balko et al.	606/108
4,550,447	A	11/1985	Seiler, Jr. et al.	623/1.32
4,553,545	A	11/1985	Maass et al.	606/198
4,560,374	A	12/1985	Hammerslag	604/509
4,562,596	A	1/1986	Kronberg	623/1.32
4,565,740	A	1/1986	Golander et al.	428/409
4,580,568	A	4/1986	Gianturco	606/198
4,613,665	A	9/1986	Larm	536/20
4,642,111	A	2/1987	Sakamoto et al.	424/492
4,655,771	A	4/1987	Wallsten	623/1.22
4,656,083	A	4/1987	Hoffman et al.	442/123
4,676,241	A	6/1987	Webb et al.	128/207.14
4,678,466	A	7/1987	Rosenwald	424/427
4,687,482	A	8/1987	Hanson	623/1.49
4,689,046	A	8/1987	Bokros	623/2.31
4,731,054	A	3/1988	Billeter et al.	604/93.01
4,733,665	A	3/1988	Palmaz	606/108
4,733,665	A	3/1988	Palmaz	606/108
4,739,762	A	4/1988	Palmaz	623/1.11
4,740,207	A	4/1988	Kreamer	623/1.15
4,749,585	A	6/1988	Greco et al.	428/422
4,753,652	A	6/1988	Langer et al.	623/1.42
4,760,849	A	8/1988	Kropf	606/191
4,768,507	A	9/1988	Fischell et al.	623/1.11
4,776,337	A	10/1988	Palmaz	623/1.11
4,786,500	A	11/1988	Wong	424/422
4,787,899	A	11/1988	Lazarus	623/1.11
4,800,882	A	1/1989	Gianturco	606/194
4,810,784	A	3/1989	Larm	536/20
4,856,516	A	8/1989	Hillstead	606/194
4,871,357	A	10/1989	Hsu et al.	604/266
4,872,867	A	10/1989	Joh	604/269
4,876,109	A	10/1989	Mayer et al.	604/269
4,886,062	A	12/1989	Wiktor	606/194
4,907,336	A	3/1990	Gianturco	29/515
4,916,193	A	4/1990	Tang et al.	525/413
4,954,126	A	9/1990	Wallsten	600/36
4,969,458	A	11/1990	Wiktor	623/1.11
4,990,131	A	2/1991	Dardik et al.	600/36
4,990,155	A	2/1991	Wilkoff	606/191
4,994,071	A	2/1991	MacGregor	606/194
4,994,298	A	2/1991	Yasuda	427/490
4,998,923	A	3/1991	Samson et al.	606/194
5,015,253	A	5/1991	MacGregor	623/1.15
5,019,090	A	5/1991	Pinchuk	623/1.15
5,019,096	A	5/1991	Fox, Jr. et al.	600/36
5,029,877	A	7/1991	Fedeli	277/354
5,034,265	A	7/1991	Hoffman et al.	442/126
5,035,706	A	7/1991	Gianturco et al.	606/198
5,041,100	A	8/1991	Rowland et al.	604/265
5,041,126	A	8/1991	Gianturco	623/1.15
5,047,020	A	9/1991	Hsu	604/266
5,049,132	A	9/1991	Shaffer et al.	604/101.02
5,049,403	A	9/1991	Larm et al.	427/2.1
5,053,048	A	10/1991	Pinchuk	623/1.43
5,059,166	A	10/1991	Fischell et al.	600/3
5,061,275	A	10/1991	Wallsten et al.	623/1.22
5,061,750	A	10/1991	Feijen et al.	525/54.1
5,064,435	A	11/1991	Porter	623/23.7
5,092,877	A	3/1992	Pinchuk	128/898
5,102,417	A	4/1992	Palmaz	606/195
5,104,404	A	4/1992	Wolff	623/1.16
5,116,365	A	5/1992	Hillstead	623/1.15
5,122,154	A	6/1992	Rhodes	623/1.13
5,131,908	A	7/1992	Dardik et al.	600/36
5,133,732	A	7/1992	Wiktor	623/1.22
5,134,192	A	7/1992	Feijen et al.	525/54.1
5,135,536	A	8/1992	Hillstead	606/195
5,163,952	A	11/1992	Froix	623/1.18
5,163,958	A	11/1992	Pinchuk	623/23.49
5,171,217	A	12/1992	March et al.	604/507
5,171,262	A	12/1992	MacGregor	623/1.15
5,176,660	A	1/1993	Truckai	604/527
5,176,972	A	1/1993	Bloom et al.	430/14
5,178,618	A	1/1993	Kandarpa	606/28
5,180,366	A	1/1993	Woods	604/96.01
5,182,317	A	1/1993	Winters et al.	523/112
5,185,408	A	2/1993	Tang et al.	525/415
5,192,307	A	3/1993	Wall	623/1.2
5,195,984	A	3/1993	Schalz	623/1.2
5,213,576	A	5/1993	Abiuso et al.	604/103.01
5,213,898	A	5/1993	Larm et al.	428/422
5,217,483	A	6/1993	Tower	623/1.15
5,222,971	A	6/1993	Willard et al.	606/198
5,226,913	A	7/1993	Pinchuk	140/71 R
5,234,456	A	8/1993	Silvestrini	623/1.2
5,246,445	A	9/1993	Yachia et al.	623/1.2
5,258,020	A	11/1993	Froix	128/898
5,258,021	A	11/1993	Duran	623/2.3
5,262,451	A	11/1993	Winters et al.	523/112
5,266,073	A	11/1993	Wall	623/1.2
5,272,012	A	12/1993	Opolski	428/423.1
5,275,622	A	1/1994	Lazarus et al.	623/1.11
5,282,823	A	2/1994	Schwartz et al.	623/1.22
5,282,824	A	2/1994	Gianturco	623/1.13
5,283,257	A	2/1994	Gregory et al.	514/458
5,288,711	A	2/1994	Mitchell et al.	424/122
5,290,305	A	3/1994	Inoue	623/1.2
5,292,331	A	3/1994	Boneau	623/1.16
5,292,802	A	3/1994	Rhee et al.	525/54.1
5,304,121	A	4/1994	Sahatjian	604/509
5,304,200	A	4/1994	Spaulding	623/1.16
5,306,250	A	4/1994	March et al.	604/104
5,308,862	A	5/1994	Ohlstein	514/411
5,308,889	A	5/1994	Rhee et al.	523/113
5,314,444	A	5/1994	Gianturco	606/195
5,314,472	A	5/1994	Fontaine	623/1.22
5,328,471	A	7/1994	Slepian	604/101.03
5,334,301	A	8/1994	Heinke et al.	204/267
5,336,518	A	8/1994	Narayanan et al.	427/470
5,338,770	A	8/1994	Winters et al.	523/112
5,342,348	A	8/1994	Kaplan	604/891.1
5,342,387	A	8/1994	Summers	606/198
5,342,621	A	8/1994	Eury	606/198
5,354,308	A	10/1994	Simon et al.	623/1.15
5,356,433	A	10/1994	Rowland et al.	424/422
5,366,504	A	11/1994	Andersen et al.	623/1.5
5,368,566	A	11/1994	Crocker	604/101.02
5,370,683	A	12/1994	Fontaine	623/1.22
5,370,691	A	12/1994	Samson	623/1.22
5,375,612	A	12/1994	Cottenceau et al.	128/899
5,376,112	A	12/1994	Duran	623/1.26
5,378,475	A	1/1995	Smith et al.	424/473
5,380,299	A	1/1995	Fearnot et al.	604/265
5,382,261	A	1/1995	Palmaz	606/158
5,383,853	A	1/1995	Jung et al.	604/103.04

5,383,928	A	1/1995	Scott et al.	623/1.12
5,387,235	A	2/1995	Chuter	623/1.11
5,389,106	A	2/1995	Tower	623/1.15
5,393,772	A	2/1995	Yue et al.	514/410
5,395,390	A	3/1995	Simon et al.	623/1.18
5,397,355	A	3/1995	Marin et al.	623/1.2
5,399,352	A	3/1995	Hanson	424/423
5,403,341	A	4/1995	Solar	606/198
5,405,377	A	4/1995	Cragg	623/1.2
5,409,696	A	4/1995	Narayanan et al.	424/78.17
5,411,549	A	5/1995	Peters	623/1.15
5,415,619	A	5/1995	Lee et al.	600/36
5,417,969	A	5/1995	Hsu et al.	424/78.27
5,419,760	A	5/1995	Narciso, Jr.	604/8
D359,802	S	6/1995	Fontaine	D24/155
5,421,955	A	6/1995	Lau et al.	216/48
5,423,885	A	6/1995	Williams	623/1.17
5,429,618	A	7/1995	Keogh	604/266
5,429,634	A	7/1995	Narciso, Jr.	604/890.1
5,439,446	A	8/1995	Barry	604/103.01
5,441,515	A	8/1995	Khosravi et al.	606/194
5,441,516	A	8/1995	Wang et al.	606/198
5,441,947	A	8/1995	Dodge et al.	514/179
5,443,458	A	8/1995	Evry	604/891.1
5,443,477	A	8/1995	Marin et al.	606/198
5,443,496	A	8/1995	Schwartz et al.	623/1.16
5,443,498	A	8/1995	Fontaine	623/1.17
5,443,500	A	8/1995	Sigwart	623/1.17
5,447,724	A	9/1995	Helmus et al.	424/426
5,449,372	A	9/1995	Schmaltz et al.	606/198
5,449,373	A	9/1995	Pinchasik et al.	606/198
5,449,382	A	9/1995	Dayton	623/1.15
5,464,450	A	11/1995	Buscemi et al.	632/1.2
5,464,540	A	11/1995	Friesen et al.	210/640
5,464,650	A	11/1995	Berg et al.	427/2.3
5,474,563	A	12/1995	Myler et al.	606/108
5,486,357	A	1/1996	Narayanan	424/78.17
5,496,365	A	3/1996	Sgro	623/1.2
5,500,013	A	3/1996	Buscemi et al.	623/1.22
5,510,077	A	4/1996	Dinh et al.	264/485
5,512,055	A	4/1996	Domb et al.	604/265
5,516,781	A	5/1996	Morris et al.	514/291
5,519,042	A	5/1996	Morris et al.	514/378
5,523,092	A	6/1996	Hanson et al.	424/423
5,527,354	A	6/1996	Fontaine et al.	623/1.17
5,545,208	A	8/1996	Wolff et al.	623/1.22
5,551,954	A	9/1996	Buscemi et al.	623/1.15
5,554,182	A	9/1996	Dinh et al.	600/36
5,554,954	A	9/1996	Takahashi	327/546
5,556,413	A	9/1996	Lam	623/1.2
5,562,922	A	10/1996	Lambert	424/486
5,563,146	A	10/1996	Morris	514/291
5,569,197	A	10/1996	Helmus	604/102.02
5,569,295	A	10/1996	Lam	606/198
5,569,462	A	10/1996	Martinson et al.	424/423
5,569,463	A	10/1996	Helmus et al.	424/426
5,571,089	A	11/1996	Crocker	604/103.01
5,571,166	A	11/1996	Dinh et al.	128/898
5,574,059	A	11/1996	Regunathan et al.	514/397
5,575,818	A	11/1996	Pinchuk	623/1.15
5,578,075	A	11/1996	Dayton	623/1.15
5,580,873	A	12/1996	Bianco et al.	514/263.36
5,580,874	A	12/1996	Bianco et al.	514/263.36
5,591,140	A	1/1997	Narayanan et al.	604/269
5,591,197	A	1/1997	Orth et al.	623/1.16
5,591,224	A	1/1997	Schwartz et al.	623/1.22
5,591,227	A	1/1997	Dinh et al.	623/1.22
5,599,352	A	2/1997	Dinh et al.	128/898
5,603,722	A	2/1997	Phan et al.	623/1.18
5,604,283	A	2/1997	Wada et al.	524/236
5,605,696	A	2/1997	Eury et al.	424/423
5,607,463	A	3/1997	Schwartz et al.	623/1.44
5,607,475	A	3/1997	Cahalan et al.	424/423
5,609,629	A	3/1997	Fearnot et al.	623/1.42
5,616,608	A	4/1997	Kinsella et al.	514/449
5,620,984	A	4/1997	Bianco et al.	514/263.36
5,621,102	A	4/1997	Bianco et al.	544/267
5,622,975	A	4/1997	Singh et al.	514/324
5,624,411	A	4/1997	Tuch	604/265
5,628,785	A	5/1997	Schwartz et al.	128/898
5,629,077	A	5/1997	Turnlund et al.	623/1.15
5,629,315	A	5/1997	Bianco et al.	514/263.36
5,632,763	A	5/1997	Glastra	623/1.15
5,632,771	A	5/1997	Boatman et al.	623/1.15
5,632,776	A	5/1997	Kurumatani et al.	424/423
5,632,840	A	5/1997	Campbell	156/196
5,635,201	A	6/1997	Fabo	424/443
5,637,113	A	6/1997	Tartaglia et al.	623/1.42
5,643,312	A	7/1997	Fischell et al.	623/1.15
5,643,939	A	7/1997	Ohlstein	514/411
5,646,160	A	7/1997	Morris et al.	514/291
5,648,357	A	7/1997	Bianco et al.	514/263.36
5,649,952	A	7/1997	Lam	623/1.15
5,649,977	A	7/1997	Campbell	623/1.15
5,651,174	A	7/1997	Schwartz et al.	29/527.2
5,652,243	A	7/1997	Bianco et al.	514/263.36
5,653,747	A	8/1997	Dereume	623/1.54
5,653,992	A	8/1997	Bezwada et al.	424/426
5,662,609	A	9/1997	Slepian	604/101.03
5,665,591	A	9/1997	Sonenshein et al.	435/375
5,665,728	A	9/1997	Morris et al.	424/122
5,667,764	A	9/1997	Kopia et al.	424/1.45
5,669,924	A	9/1997	Shaknovich	623/1.11
5,670,506	A	9/1997	Leigh et al.	514/141
5,672,638	A	9/1997	Verhoeven et al.	523/112
5,674,242	A	10/1997	Phan et al.	606/198
5,679,400	A	10/1997	Tuch	427/2.14
5,679,659	A	10/1997	Verhoeven et al.	514/56
5,684,061	A	11/1997	Ohnishi et al.	523/114
5,691,311	A	11/1997	Maraganore et al.	514/12
5,693,085	A	12/1997	Buirge et al.	623/1.13
5,697,967	A	12/1997	Dinh et al.	128/898
5,697,971	A	12/1997	Fischell et al.	623/1.15
5,700,286	A	12/1997	Tartaglia et al.	623/1.15
5,707,385	A	1/1998	Williams	606/192
5,709,874	A	1/1998	Hanson et al.	424/423
5,713,949	A	2/1998	Jayaraman	623/1.12
5,716,981	A	2/1998	Hunter et al.	514/449
5,725,549	A	3/1998	Lam	623/1.15
5,725,567	A	3/1998	Wolff et al.	623/1.42
5,728,150	A	3/1998	McDonald et al.	623/1.15
5,728,420	A	3/1998	Keogh	427/2.12
5,731,326	A	3/1998	Hart et al.	514/323
5,733,327	A	3/1998	Igaki et al.	623/1.5
5,733,920	A	3/1998	Mansuri et al.	514/337
5,733,925	A	3/1998	Kunz et al.	514/449
5,735,897	A	4/1998	Buirge	623/1.15
5,739,138	A	4/1998	Bianco et al.	514/263.36
5,755,734	A	5/1998	Richter et al.	606/194
5,755,772	A	5/1998	Evans et al.	128/898
5,759,205	A	6/1998	Valentini	433/173
5,769,883	A	6/1998	Buscemi et al.	623/1.42
5,776,184	A	7/1998	Tuch	623/1.11
5,780,476	A	7/1998	Underiner et al.	514/263.36
5,782,908	A	7/1998	Cahalan et al.	623/1.13
5,788,979	A	8/1998	Alt et al.	424/426
5,792,106	A	8/1998	Mische	604/103.01
5,792,772	A	8/1998	Bianco et al.	514/263.36
5,798,372	A	8/1998	Davies et al.	514/356
5,799,384	A	9/1998	Schwartz et al.	29/458
5,800,507	A	9/1998	Schwartz	623/1.11
5,800,508	A	9/1998	Goicoechea et al.	623/1.15
5,807,861	A	9/1998	Klein et al.	514/263.35
5,811,447	A	9/1998	Kunz et al.	514/411
5,820,917	A	10/1998	Tuch	427/2.1
5,820,918	A	10/1998	Ronan et al.	427/2.1

5,824,048	A		10/1998	Tuch 128/898
5,824,049	A		10/1998	Ragheb et al. 623/1.44
5,827,587	A		10/1998	Fukushi 428/36.6
5,833,651	A		11/1998	Donovan et al. 604/509
5,837,008	A		11/1998	Berg et al. 128/898
5,837,313	A		11/1998	Ding et al. 427/2.21
5,843,120	A		12/1998	Israel et al. 623/1.15
5,843,166	A		12/1998	Lentz et al. 623/1.13
5,843,172	A		12/1998	Yan 623/1.42
5,849,034	A		12/1998	Schwartz 606/36
5,851,217	A		12/1998	Wolff et al. 606/191
5,851,231	A		12/1998	Wolff et al. 623/1.42
5,858,990	A		1/1999	Walsh 514/44
5,861,027	A		1/1999	Trapp 623/1.15
5,865,814	A		2/1999	Tuch 623/1.15
5,871,535	A		2/1999	Wolff et al. 128/898
5,873,904	A		2/1999	Ragheb et al. 623/1.13
5,876,433	A		3/1999	Lunn 623/1.15
5,877,224	A		3/1999	Brocchini et al. 514/772.2
5,879,697	A		3/1999	Ding et al. 424/422
5,882,335	A		3/1999	Leone et al. 604/103.02
5,891,108	A		4/1999	Leone et al. 604/264
5,893,840	A		4/1999	Hull et al. 604/103.02
5,897,911	A		4/1999	Loeffler 427/2.25
5,900,246	A		5/1999	Lambert 424/429
5,902,266	A		5/1999	Leone et al. 604/509
5,916,910	A		6/1999	Lai 514/423
5,922,393	A		7/1999	Jayaraman 427/2.3
5,932,243	A		8/1999	Fricker et al. 424/450
5,932,299	A		8/1999	Katoot 427/508
5,932,580	A		8/1999	Levitzki et al. 181/152
5,951,586	A		9/1999	Berg et al. 606/198
5,957,971	A		9/1999	Schwartz 623/1.15
5,968,091	A		10/1999	Pinchuk et al. 623/1.16
5,972,027	A		10/1999	Johnson 623/1.42
5,976,534	A		11/1999	Hart et al. 424/145.1
5,977,163	A		11/1999	Li et al. 514/449
5,980,553	A		11/1999	Gray et al. 623/1.15
5,980,566	A		11/1999	Alt et al. 623/23.7
5,980,972	A		11/1999	Ding 427/2.24
5,981,568	A		11/1999	Kunz et al. 514/411
5,985,307	A		11/1999	Hanson et al. 424/423
5,997,468	A		12/1999	Wolff et al. 606/36
6,004,346	A		12/1999	Wolff et al. 623/23.71
6,015,432	A		1/2000	Rakos et al. 623/1.13
6,039,721	A		3/2000	Johnson et al. 604/508
6,059,813	A		5/2000	Vrba et al. 606/198
6,071,305	A		6/2000	Brown et al. 623/1.43
6,074,659	A		6/2000	Kunz et al. 424/423
6,080,190	A		6/2000	Schwartz et al. 623/1.22
6,096,070	A		8/2000	Ragheb et al. 623/1.39
6,120,536	A		9/2000	Ding et al. 623/1.43
6,120,847	A		9/2000	Yang et al. 427/335
6,136,798	A		10/2000	Cody et al. 514/141
6,140,127	A		10/2000	Sprague 435/395
6,146,358	A		11/2000	Rowe 604/103
6,153,252	A	*	11/2000	Hossainy et al. 427/2.3
6,159,488	A		12/2000	Nagier et al. 424/423
6,171,232	B1		1/2001	Papandreou et al. 600/36
6,171,609	B1		1/2001	Kunz 424/422
6,177,272	B1		1/2001	Nabel et al. 435/320.1
6,179,817	B1		1/2001	Zhong 604/265
6,193,746	B1		2/2001	Strecker 623/1.13
6,214,901	B1		4/2001	Chudzik et al. 523/113
6,225,346	B1		5/2001	Tang et al. 514/523
6,240,616	B1		6/2001	Yan 29/527.2
6,245,537	B1		6/2001	Williams et al. 435/135
6,251,920	B1		6/2001	Grainger et al. 514/319
6,254,632	B1		7/2001	Wu et al. 623/1.15
6,254,634	B1		7/2001	Anderson et al. 623/1.42
6,258,121	B1		7/2001	Yang et al. 623/1.46
6,268,390	B1		7/2001	Kunz 514/411
6,273,913	B1		8/2001	Wright et al. 623/1.42
6,284,305	B1		9/2001	Ding et al. 427/2.28
6,287,320	B1		9/2001	Slepian 606/194
6,287,628	B1		9/2001	Hossainy et al. 427/2.3
6,299,604	B1		10/2001	Ragheb et al. 604/265
6,306,144	B1		10/2001	Sydney et al. 606/108
6,306,166	B1		10/2001	Barry et al. 623/1.46
6,306,176	B1		10/2001	Whitbourne 623/23.59
6,306,421	B1		10/2001	Kunz et al. 424/423
6,309,380	B1		10/2001	Larson et al. 604/502
6,309,660	B1		10/2001	Hsu et al. 424/425
6,313,264	B1		11/2001	Caggiano et al. 530/350
6,316,018	B1		11/2001	Ding et al. 424/423
6,335,029	B1		1/2002	Kamath et al. 424/423
6,358,556	B1		3/2002	Ding et al. 427/2.24
6,369,039	B1		4/2002	Palasis et al. 424/93.2
6,379,382	B1		4/2002	Yang 623/1.42
6,387,121	B1		5/2002	Alt 623/1.15
6,403,635	B1		6/2002	Kinsella et al. 514/449
6,407,067	B1		6/2002	Schafer 514/19
6,517,858	B1		2/2003	Le Moel et al. 424/424
6,517,889	B1		2/2003	Jayaraman 427/2.24
6,545,097	B2		4/2003	Pinchuk et al. 525/240
6,585,764	B2		7/2003	Wright et al. 623/1.42
6,620,194	B2		9/2003	Ding et al. 623/1.43
6,746,773	B2		6/2004	Llanos et al. 428/421
6,776,796	B2		8/2004	Llanos et al. 623/1.46
6,808,536	B2		10/2004	Wright et al. 623/1.42
2001/0007083	A1		7/2001	Roorda 623/1.15
2001/0029351	A1		10/2001	Falotico et al. 604/103.02
2001/0029660	A1		10/2001	Johnson 29/557
2001/0032014	A1		10/2001	Yang et al. 623/1.15
2001/0034363	A1		10/2001	Li et al. 514/449
2001/0037145	A1		11/2001	Guruwaiya et al. 623/1.15
2002/0010418	A1		1/2002	Lary et al. 604/101.04
2002/0032477	A1		3/2002	Helmus et al. 623/1.2
2002/0041899	A1		4/2002	Chudzik et al. 424/487
2002/0061326	A1		5/2002	Li et al. 424/424
2002/0068969	A1		6/2002	Shanley et al. 623/1.16
2002/0071902	A1		6/2002	Ding et al. 427/2.24
2002/0082680	A1		6/2002	Shanley et al. 623/1.16
2002/0082685	A1		6/2002	Sirhan et al. 623/1.42
2002/0091433	A1		7/2002	Ding et al. 623/1.2
2002/0095114	A1		7/2002	Palasis 604/96.01
2002/0099438	A1		7/2002	Furst 623/1.16
2002/0103526	A1		8/2002	Steinke 623/1.11
2002/0119178	A1		8/2002	Levesque et al. 424/423
2002/0123505	A1		9/2002	Mollison et al. 514/291
2002/0127327	A1		9/2002	Schwartz et al. 427/2.15
2002/0133222	A1		9/2002	Das 623/1.16
2002/0133224	A1		9/2002	Bajgar et al. 623/1.39
2002/0165608	A1		11/2002	Llanos 604/500
2002/0193475	A1		12/2002	Hossainy et al. 524/113
2003/0065377	A1		4/2003	Davila et al. 604/265
2003/0216699	A1		11/2003	Falotico 604/265
2004/0049265	A1		3/2004	Ding et al. 623/1.42
2004/0243097	A1		12/2004	Falotico et al. 604/500
2004/0260268	A1		12/2004	Falotico et al. 604/500
2005/0002986	A1		1/2005	Falotico et al. 424/426
2005/0004663	A1		1/2005	Llanos et al. 623/1.46
2005/0033261	A1		2/2005	Falotico et al. 604/500
2005/0106210	A1		5/2005	Ding et al. 424/423
2005/0187611	A1		8/2005	Ding et al. 623/1.15
2005/0208200	A1		9/2005	Ding et al. 427/2.25
2006/0088654	A1		4/2006	Ding et al. 427/2.21
2006/0089705	A1		4/2006	Ding et al. 623/1.15

FOREIGN PATENT DOCUMENTS

DE	19723723 A1	12/1998
EP	0 145 166 A2	6/1985
EP	0 177 330 A2	4/1986
EP	0 183 372 A1	6/1986
EP	0 221 570 A2	5/1987

EP	0 421 729 A2	4/1991
EP	0 540 290 A2	5/1993
EP	0 568 310 A1	11/1993
EP	0 604 022 A1	6/1994
EP	0 621 015 A1	10/1994
EP	0 623 354 A1	11/1994
EP	0 734 698 A2	3/1996
EP	0 712 615 A1	5/1996
EP	0 716 836 A1	6/1996
EP	0 734 721 A2	10/1996
EP	0 747 069 A2	12/1996
EP	0 761 251 A1	3/1997
EP	0 800 801 A1	10/1997
EP	0 540 290 B1	1/1998
EP	0 830 853 A1	3/1998
EP	0 815 803 A1	7/1998
EP	0 850 651 A2	7/1998
EP	0 938 878 A2	9/1999
EP	0 938 878 A3	9/1999
EP	0 950 386 A2	10/1999
EP	0 968 688 A1	1/2000
EP	0 633 032 B1	2/2001
EP	1 192 957 A2	4/2002
EP	1 588 726 A1	10/2005
EP	1 588 727 A1	10/2005
FR	566 807 A1	4/1992
GB	0 662 307 A2	12/1951
GB	1 205 743 A	9/1970
GB	2 135 585 A	9/1984
SU	660689	5/1979
SU	1457921	2/1989
WO	89/03232 A1	4/1989
WO	91/12779 A1	9/1991
WO	92/15286 A1	9/1992
WO	94/01056 A1	1/1994
WO	94/21308 A1	9/1994
WO	94/21309 A1	9/1994
WO	94/24961 A1	11/1994
WO	96/00272 A1	1/1996
WO	96/26689 A1	9/1996
WO	96/32907 A1	10/1996
WO	96/34580 A1	11/1996
WO	97/25000 A1	7/1997
WO	97/33534 A1	9/1997
WO	98/08463 A1	3/1998
WO	98/13344 A1	4/1998
WO	98/19628 A1	5/1998
WO	98/23228 A1	6/1998
WO	98/23244 A1	6/1998
WO	98/34669 A1	8/1998
WO	98/36784 A1	8/1998
WO	98/47447 A1	10/1998
WO	98/56312 A1	12/1998
WO	00/21584 A1	4/2000
WO	00/27445 A1	5/2000
WO	00/27455 A1	5/2000
WO	00/32255 A1	6/2000
WO	00/38754 A1	7/2000
WO	01/87342 A2	11/2001
WO	01/87372 A1	11/2001
WO	01/87373 A1	11/2001
WO	01/87376 A1	11/2001
WO	02/26139 A1	4/2002
WO	02/26271 A1	4/2002
WO	02/26280 A1	4/2002
WO	02/26281 A1	4/2002
WO	03/015664 A1	2/2003
WO	03/057218 A1	7/2003

OTHER PUBLICATIONS

U.S. Appl. No. 08/424,884, filed Apr. 19, 1995, Helmus et al.
U.S. Appl. No. 08/526,273, filed Sep. 11, 1995, Ding.
U.S. Appl. No. 08/730,542, filed Oct. 11, 1996, Helmus.
U.S. Appl. No. 09/575,480, filed May 19, 2000, Kopia.
U.S. Appl. No. 10/431,059, filed May 7, 2003, Falotico.
U.S. Appl. No. 10/829,074, filed Apr. 21, 2004, Falotico et al.
U.S. Appl. No. 10/833,200, filed Apr. 27, 2004, Falotico et al.
U.S. Appl. No. 10/852,517, filed May 24, 2004, Falotico et al.

Abraham, R. T., "Mammalian target of rapamycin: Immunosupressive drugs offer new insight into cell growth regulation," *Progress in Inflammation Research*, 2000, Switzerland.

Alvarado, R. et al., "Evaluation of Polymer-coated Balloon-expandable Stents in Bile Ducts," *Radiology*, 1989, 170, 975-978.

Badimon, J. J. et al., "Inhibitory Effects of Rapamycin on Intimal Hyperplasia After PTCA," *JACC*, Mar. 1998.

Bailey et al., "Polymer Coating of Palmaz-Schatz Stent Attenuates Vascular Spasm after Stent Placement," *Circulation*, 82:III-541 (1990).

Berk, B. C. et al., "Pharmacologic Roles of Heparin and Glucocorticoids to Prevent Restenosis After Coronary Angioplasty," *JACC*, May 1991, 17(6), 111B-117B.

Bertram, P. G. et al., "The 14-3-3 proteins positively regulate rapamycin-sensitive signaling," *Current Biology*, 1998, 8, 1259-1267.

Biomaterials Science (B.D. Ratner, Ed.), Academic Press, New York, NY, pp. 228-238, 1996.

Campbell, G. R. et al., "Phenotypic Modulation of Smooth Muscle Cells in Primary Culture, Vascular Smooth Muscle Cells in Culture," *CRC Press*, 1987, 39-55.

Chang, M. W. et al., "Adenovirus-mediated Over-expression of the Cyclin/Cyclin-dependent Kinase inhibitor, p21 inhibits Vascular Smooth Muscle Cell Proliferation and Neointima Formation in the Rat Carotid Artery Model of Balloon Angioplasty," *J. Clin. Invest.*, 1995, 96, 2260-2268.

Chung, J. et al., "Rapamycin-FKBP specifically blocks growth-dependent activation of and signaling by the 70 kd S6 protein kinases," *Cell*, Jun. 26, 1992, 69(7), 1227-1236.

Clowes, A. W. et al., "Kinetics of cellular proliferation after arterial injury. IV. Heparin inhibits rat smooth muscle mitogenesis and migration," *Circ. Res.*, 1986, 58(6), 839-845.

Clowes, A. W. et al., Kinetics of Cellular Proliferation after Arterial Injury, *Laboratory Investigation*, 1985, 52(6), 611-616.

Clowes, A. W. et al., "Significance of quiescent smooth muscle migration in the injured rat carotid artery," *Circ Res.* 1985, 56(1), 139-145.

Clowes, A. W., "Suppression by heparin of smooth muscle cell proliferation in injured arteries," *Nature*, 1977, 265(5595), 625-626.

Colburn, M. D. et al., "Dose responsive suppression of myointimal hyperplasia by dexamethasone," *J. Vasc. Surg.*, 1992, 15, 510-518.

Currier, J. W. et al., "Colchicine Inhibits Restenosis After Iliac Angioplasty in the Atherosclerotic Rabbit," *Circ.*, 1989, 80(4), 11-66 (Abstract No. 0263).

Encyclopedia of Polymer Science and Engineering, vol. 7, Fluorocarbon Elastomers, p. 257-267, Mar. 1989.

Farb, A. et al., "Vascular smooth muscle cell cytotoxicity and sustained inhibition of neointimal formation by fibroblast growth factor 2-saporin fusion protein," *Circ. Res.*, 1997, 80, 542-550.

Ferns, G. A. A. et al., "Inhibition of Neointimal Smooth Muscle Accumulation After Angioplasty by an Antibody to PDGF," *Science*, 1991, 253, 1129-1132.

Fischman, D. L. et al., "A Randomized Comparison of Coronary-Stent Placement and Balloon Angioplasty in the Treatment of Coronary Artery Disease," *N. Eng. J. Med.*, 1994 Aug. 25, 331(8), 496-501.

Franklin, S. M. et al., "Pharmacologic prevention of restenosis after coronary angioplasty: review of the randomized clinical trials," *Coronary Artery Disease* Mar. 1993, 4(3), 232-242.

Fukuyama, J. et al., "Tranilast suppresses the vascular intimal hyperplasia after balloon injury in rabbits fed on a high-cholesterol diet," *Eur. J. Pharmacol.*, 1996, 318, 327-332.

Gregory, C. R. et al., "Rapamycin Inhibits Arterial Intimal Thickening Caused by Both Alloimmune and Mechanical Injury," *Transplantation*, Jun. 1993, 55(6), 1409-1418.

Gregory, C. R. et al, "Treatment with Rapamycin and Mycophenolic Acid Reduces Arterial Intimal Thickening Produced by Mechanical Injury and Allows Endothelial Replacement," *Transplantation*, Mar. 15, 1995, 59(5), 655-661.
Guyton, J. R. et al., "Inhibition of rat arterial smooth muscle cell proliferation by heparin. In vivo studies with anticoagulant and nonanticoagulant heparin," *Circ. Res.*, 1980, 46, 625-634.
Hansson, G. K. et al., "Interferon-γ Inhibits Arterial Stenosis After Injury," *Circ.*, 1991, 84, 1266-1272.
Hashemolhosseini, S. et al., "Rapamycin Inhibition of the G1 to S Transition Is Mediated by Effects on Cyclin D1 mRNA and Protein Stability," *J Biol Chem*, Jun. 5, 1998, 273, 14424-14429.
Jonasson, J. et al., "Cyclosporin A inhibits smooth muscle proliferation in the vascular response to injury," *Proc. Natl., Acad. Sci.*, 1988, 85, 2303-2306.
Kuhnt, M. et al., "Microbial Conversion of Rapamycin," *Enzyme and Microbial Technology*, 1997, 21, 405-412.
Lange, R. A. MD et al., "Restenosis After Coronary Balloon Angioplasty," *Annu. Rev. Med.*, 1991, 42, 127-132.
Liu, M. W. et al., "Trapidil in Preventing Restenosis After Balloon Angioplasty in the Atherosclerotic Rabbit," *Circ.*, 1990, 81, 1089-1093.
Liu, M. W., MD et al., "Restenosis After Coronary Angioplasty Potential Biologic Determinants and Role of Intimal Hyperplasia," *Circulation*, 1989, 79, 1374-1387.
Lundergan, C. F. et al., "Peptide inhibition of Myointimal Proliferation by Angiopeptin, a Somatostatin Analogue," *JACC*, May 1991, 17(6), 132B-136B.
Majesky, M. W. et al., "Heparin regulates smooth muscle S phase entry in the injured rat carotid artery," *Circ. Res.*, 1987, 61, 296-300.
Marx, S. O. et al., "Rapamycin-FKBP Inhibits Cell Cycle Regulators of Proliferation in Vascular Smooth Muscle Cells," *Circ. Res.*, 1995, 76, 412-417.
Nemecek, G. M. et al., "Terbinafine Inhibits the Mitogenic Response to Platelet-Derived Growth Factor in Vitro and Neoinimal Proliferation in Vivo," *J. Pharmacol. Exp. Thera.*, 1989, 248, 1167-1174.
Okada, T. et al., "Localized Release of Perivascular Heparin Inhibits Intimal Proliferation after Endothelial Injury without Systemic Anticoagulation," *Neurosurgery*, 1989, 25, 892-898.
Poon, M. et al., "Rapamycin Inhibits Vascular Smooth Muscle Cell Migration," *J. Clin Invest.*, Nov. 1996, 98(10), 2277-2283.
Popma, J. J. et al., "Clinical trials of restenosis after coronary angioplasty," *Circulation*, Sep. 1991, 84(3), 1426-1436.
Powell, J. S. et al., "Inhibitors of Angiotensin-Converting Enzyme Prevent Myointimal Proliferation After Vascular Injury," *Science*, 1989, 245, 186-188.
Rensing, B. J. et al., Coronary restenosis elimination with a sirolimus eluting stent, *European Heart Journal*, 2001, 22, 2125-2130.
Rodeck, C. et al., "Methods for the Transcervical Collection of Fetal Cells During the First Trimester of Pregnancy," *Prenatal Diagnosis*, 1995, 15, 933-942.
Ruef, J. MD, et al., "Flavopiridol Inhibits Muscle Cell Proliferation In Vitro and Neointimal Formation In Vivo After Carotid Injury in the Rat," From the Division of Cardiology and Sealy Center for Molecular Cardiology, University of Texas Medical Branch, Galveston; Accepted Apr. 9, 1999; *Circulation* Aug. 10, 1999, pp. 659-665.
Serruys, P. W. et al., "A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease," *N Engl J Med*, Aug. 25, 1994; 331(8), 489-495.
Serruys, P. W. et al., "Evaluation of ketanserin in the prevention of restenosis after percutaneous transluminal coronary angioplasty. A multicenter randomized double-blind placebo-controlled trial," *Circulation*. Oct. 1993; 88(4 Pt 1), 1588-1601.
Serruys, P. W. et al., "Heparin-coated Palmaz-Schatz stents in human coronary arteries. Early outcome of the Benestent-II Pilot Study," *Circulation*, Feb. 1, 1996; 93(3), 412-422.
Siekierka, J. J., "Probing T-Cell Signal Transduction Pathways with the Immunosupressive Drugs, FK-506 and Rapamycin," *Immunologic Research*, 1994, 13, 110-116.
Sigwart, et al., "Intravascular Stents to Prevent Occlusion and Restenosis After Transluminal Angioplasty," *N. Engl. J. Med.*, Mar. 19, 1987, 316, 701-706.
Simons, M. et al., "Antisense c-*myb* oligonucleotides inhibit intimal arterial smooth muscle cell accumulation in vivo," *Nature*, 1992, 359, 67-70.
Snow, A. D. et al., "Heparin modulates the composition of the extracellular matrix domain surrounding arterial smooth muscle cells," *Am. J. Pathol.*, 1990, 137, 313-330.
Sollott, S. J. et al., "Taxol Inhibits Neointimal Smooth Muscle Cell Accumulation after Angioplasty in the Rat," *J. Clin. Invest.*, 1995, 95, 1869-1876.
van Der Giessen, et al., "Self-expandable Mesh Stents: an Experimental Study Comparing Polymer Coated and Uncoated Wallstent Stents in the Coronary Circulation of Pigs," *Circulation* 1990, 82(suppl. III):III-542.
van Der Giessen, W. J. et al., "Coronary stenting with polymer-coated and uncoated self-expanding endoprostheses in pigs," Coron. Art. Disease 1992; 3, 631-640.
Vasey, C. G. et al., "Clinical Cardiology: Stress Echo and Coronary Flow", , *Circulation*, Oct. 1989, 80(4) Supplement II, II-66.
Verweire, E. et al., "Evaluation of Fluorinated Polymers As Coronary Stent Coating," *Journal of Materials Science: Materials in Medicine*, Apr. 2000.
Weinberger, J. et al., "Intracoronary irradiation: dose response for the prevention of restenosis in swine," *Int. J. Rad. Onc. Biol. Phys.*, 1996, 36, 767-775.
Preliminary Amendment in U.S. Appl. No. 07/258,189, May 22, 1989.
Trial Transcript from Nov. 6, 2000 at 185-90 and 235-36 (Attorneys' opening remarks regarding '984 patent).
Trial Transcript from Nov. 7, 2000 at 274-301, 307-315, 320-28 and 332 (Cordis expert testimony regarding the Palmaz-Schatz stent); 370-379, 480-496 (J. Palmaz testimony regarding the Palmaz-Schatz stent, the '984 patent and the connected z-stent art).
Trial Transcript from Nov. 8, 2000 at 547-63, 657-63, 674-722, 782-85 (Cordis expert testimony regarding the Palmaz-Schatz stent, the '984 patent and the connected z-stent art).
Trial Transcript from Nov. 9, 2000 at 819-23, 921 (Cordis expert testimony regarding the '984 patent); 926-941 . (R. Croce testimony re Palmaz-Schatz stent); 1033-1053. (R. Schatz testimony).
Trial Transcript from Nov. 13, 2000 at 1086-1 134. (R. Schatz testimony); 1275-1305 (Cordis expert testimony regarding the '984 patent).
Trial Transcript from Nov. 14, 2000 at 1390-1404, 1448-1454, 1486-1500 (Cordis expert testimony regarding the '984 patent).
Trial Transcript from Nov. 15, 2000 at 1686-87, 1724-42, 1828-34, 1850-54, 1887-92 (AVE expert testimony regarding the '984 patent).
Trial Transcript from Nov. 16, 2000 at 2077-198 (AVE expert testimony regarding the alleged obviousness of the '984 patent).
Trial Transcript from Nov. 17, 2000 at 2331-34 (jury instructions as to the meaning of the limitations of the claims of the '984 patent).
Trial Transcript from Nov. 20, 2000 at 2441-48, 2499-2500, 2546-50, 2552-56 (Attorneys' closing arguments regarding the '984 patent).
Trial Transcript from Nov. 21, 2000 at 2592-94 (reading of jury verdict).
Trial Transcript from Dec. 18, 2000 at 2750-95 (Cordis expert testimony regarding the Palmaz-Schatz stent during the damages phase).
Trial Transcript from Dec. 20, 2000 at 3421-88)AVE expert testimony regarding the Palmaz-Schatz stent during the damages phase).
Jury verdict, dated Nov. 21, 2000.
District Court decisions on post-trial motions (194 F. Supp. 2d 323).
Court of Appeal for the Federal Circuit decision (339 F.3d 1352).
Trial Transcript from Mar. 4, 2005 at 133-135, 171-173 and 192-96 (Attorney's opening remarks regarding '984 validity).
Trial Transcript from Mar. 7, 2005 at 275-31 1 (Cordis expert testimony regarding the Palmaz-Schatz stent); 342-46, 353-59, 416-425 (J. Palmaz testimony regarding the Palmaz-Schatz stent, the '984 patent and the connected z-stent art); 430-449, 452-58,

462-492 (R. Croce testimony regarding the Palmaz-Schatz stent); 500-507 (Cordis expert testimony regarding the '984 patent).
Trial Transcript from Mar. 8, 2005 at 609 (Cordis expert testimony regarding the '984 patent); 628-73, 724-740, 773, 801-839 (Cordis expert testimony regarding the '984 patent, the prior art and the Palmaz-Schatz stent).
Trial Transcript from Mar. 9, 2005 at 936-49, 968-69 (Cordis expert testimony regarding the '984 patent, the prior art and the Palmaz-Schatz stent).
Trial Transcript from Mar. 10, 2005 at 1427-74, 178-1509, 1514-23 (AVE expert testimony regarding the alleged obviousness of the '984 patent); 1566-93 (AVE expert testimony regarding Palmaz-Schatz stent); 1634-49 (R. Schatz testimony).
Trial Transcript from Mar. 11, 2005 at 1846-47, 1891-1900, 1919 (Attorneys' closing arguments regarding '984 obviousness).
Trial Transcript from Mar. 14, 2005 at 1964-67 (reading of jury verdict).
Jury verdict dated Mar. 14, 2005.
Medtronic Vascular Inc.'s Opening Brief in Support of Its Motion for Judgment As A Infringement Claim dated Apr. 19, 2005.
Medtronic Vascular Inc.'s Opening Brief in Support of Its Motion for a New Trial dated Apr. 19, 2005.
D.I. 1407, Cordis' Combined Answering Brief In Opposition to AVE's Motion for JMOL on Infringement of the Palmaz '762 and Schatz '984 Patents and Its Motion for a New Trial dated May 5, 2005.
D.I. 1414, Medtronic Vascular Inc.'s Combined Reply Brief In Support of Its Motion for Judgment as a Matter of Law on Cordis Corp.'s Patent Infringement Claims and Its Motion for a New Trial dated May 19, 2005.
Trial Transcript from Feb. 8, 2001 at 372-412, 449-469 (B. Tobor testimony regarding the prosecution of the '417, '984 and '332 patents); 510-13 (J. Milnamow testimony regarding the prosecution of the '332 patent); 558-604 (J. Palmaz testimony regarding the prosecution of the '417, '984 and '332 patents and the prior art).
Trial Transcript from Feb. 9, 2001 at 637-45, 662-672, 682-85 (J. Palmaz testimony regarding the prior art); 699-742 (R. Schatz testimony); 769-770, 790-95 (Cordis expert testimony regarding prior art).
D.I. 1067, Medtronic AVE, Inc.'s Post-Trial Brief Relating to the Unenforceability of the '762 and '984 Patents Due to Inequitable Conduct.
D.I. 1077, Cordis' Combined Answering Brief in Opposition to AVE's BSC's Post-Hearing Briefs on Alleged Inequitable Conduct Concerning the '762, '984 and '332 Patents.
D.I. 1089, Reply Brief In Support of Medtronic AVE, Inc.'s Contention that the '762 and '984 Patents are Unenforceable Due to Inequitable Conduct dated May 7, 2001.
C.A. No. 00-886-SLR, Answer and Counterclaims of Def. Medtronic AVE, Inc. To First Amended Complaint of Plaintiff Cordis Corp.
BSC's Opening Post-Trial Brief in Support of Its Defense That the Patents in Suit Are Unenforceable, dated Mar. 16, 2001.
Reply Brief in Support of BSC's Defense That the Patents in Suit Are Unenforceable, dated May 7, 2001.
Court's Decision on allegations of inequitable conduct (194 F. Supp. 2d 323) Mar. 28, 2002.
Trial Transcript from Nov. 21, 2000 at 155-57 and 180-84 (Attorneys' opening remarks regarding '332 patent).
Trial Transcript from Nov. 27, 2000 at 227-51, 260-300 (Cordis expert testimony regarding the Palmaz-Schatz stent); 343-60, 363-67, 424-33 (J. Palmaz testimony regarding the Palmaz-Schatz stent and the '332 patent).
Trial Transcript from Nov. 28, 2000 at 649-71.
Trial Transcript from Nov. 29, 2000 at 791-816, 859-870, 953-62 (Cordis expert testimony regarding the '332 patent and the Palmaz-Schatz stent).
Trial Transcript from Nov. 30, 2000 at 1018 (Cordis expert testimony regarding the '332 patent); 1062-80, 1 108-1 1 1 1 (R. Croce testimony regarding the Palmaz-Schatz stent); 1 169-70, 1205-17, 1236-45 (Cordis expert testimony regarding the '332 patent).
Trial Transcript from Dec. 1, 2000 at 1352-54 (Cordis expert testimony regarding the '332 patent); 1364-1442 (R. Schatz testimony); 1493-1508, 1552-69 (BSC expert testimony regarding the '332 patent and the Palmaz-Schatz stent).
Trial Transcript from Dec. 4, 2000 at 1602-12, 1638-51, 1713-14, 1730-61, 1811-14, 1823-36 (BSC expert testimony regarding the alleged obviousness of the '332 patent, the prior art and the Palmaz-Schatz stent).
Trial Transcript from Dec. 6, 2000 at 2318-27, 2342-58 (BSC expert testimony regarding the '332 patent).
Trial Transcript from Dec. 7, 2000 at 2549-52 (Cordis expert testimony regarding the '332 patent); 2575-2579, 2591-92, 2630-31, 2649, 2669-71, 2684-85, 2688, 2708-10, 2725-27 (Attorney closing argument regarding '332 patent); 2742-46 Q'ury instructions as to the meaning of the limitations of the claims of the '332 patent).
Trial Transcript from Dec. 11, 2000 at 2817-22 (reading of jury verdict).
Jury verdict, dated Dec. 11, 2000.
D.I. 699, Motion by Defendant BSC and Scimed Life Systems, Inc. For Summary Judgment of Invalidity of U. S. Appl. No. 5,902,332 dated Apr. 4, 2000.
D.I.896, Order Denying Motion for Summary Judgment of Invalidity and Unenforceability of Claims 1, 3, and 5 of the U.S. Appl. No. 5,902,332 Denying {699-1} Motion for Summary Judgment of Invalidity of U.S. Appl. No. 5,902,332 dated Oct. 12, 2000.
Wright et al., Percutaneous Endovascular Stent: An Experimental Study (Abstract), RSNA Meeting (Nov. 28, 1984).
Hearing Transcript from Feb. 10, 1998 at 122-32, 146-80 (Attorneys' opening remarks regarding '417 patent); 180-312 (R. Schatz testimony) [Portions of This Transcript Have Been Removed as Confidential].
Hearing Transcript from Feb. 11, 1998 at 427-575, 577-651 (Cordis expert testimony regarding the '417 patent, the prior art and the Palmaz-Schatz stent).
Hearing Transcript from Feb. 13, 1998 at 1121-1261 (Guidant expert testimony regarding the alleged obviousness of the '417 patent, the prior art and the Palmaz-Schatz stent). [Portions of This Transcript Have Been Removed as Confidential].
Order by J. Robinson denying Cordis' Motion for a Preliminary Injuction Against ACS dated Jul. 17, 1998.
ACS, Inc.'s and Guidant Corp.'s Opening Brief in Support of Their Motion for Summary Judgment of Invalidity of U.S. Appl. No. 5,102,417 dated Aug. 27, 1998.
Plaintiff's Answering Brief in Opposition to ACS' and BSC's Motion for Summary Judgment on Obviousness dated Sep. 24, 1998.
Order dated Mar. 31, 2000.
Schatz Deposition Testimony; May 15, 1996: 79-83, 89-92, 105-107 and 153-161.
Schatz Deposition Testimony; May 16, 1996: 555-564, 569-572.
Schatz Deposition Testimony; Jan. 8, 1998: 67-73, 108-110.
Schatz Deposition Testimony; Jul. 14, 1998: 69-77, 108-112, 119-123.
Schatz Deposition Testimony; Jul. 12, 1999: 88-91, 132-135, 144-149, 218-223, 231-242.
Schatz Deposition Testimony; Jul. 13, 1999: 251-334, 339-345, 374-416.
Schatz Deposition Testimony; Jul. 14, 1999: 454-550.
Schatz Deposition Testimony; Jul. 15, 1999: 560-614.
Schatz Deposition Testimony; Dec. 2, 1999: 906-91 1, 928-942, 945-963, 976-978, 1029-1034, 1038-1042.
Palmaz Deposition Testimony, Nov. 5, 1991: 160-172.
Palmaz Deposition Testimony, Feb. 5, 1995: 710-727.
Palmaz Deposition Testimony, Jul. 16, 1998: 55-56, 81-82.
Palmaz Deposition Testimony, Jul. 28, 1999: 560-568, 570-579.
Palmaz Deposition Testimony, Jul. 29, 1999: 778-785.
Palmaz Deposition Testimony, Aug. 31, 1999: 1403-1452.
Palmaz Deposition Testimony, Sep. 2, 1999: 1953-1960.
Palmaz Deposition Testimony, Oct. 14, 1999: 2201-2209; 2275-2342; 2371-2411.
Palmaz Deposition Testimony, Oct. 15, 1999: 2424-2497; 2508-2589.
Palmaz Deposition Testimony, Oct. 16, 1999: 2853-2860.
Tobor Deposition Testimony, Jun. 17, 1999: 837-958.

Tobor Deposition Testimony, Jun. 18, 1999: 1095-1184.
Tobor Deposition Testimony, Dec. 1, 1999: 1217-1371.
Tobor Deposition Testimony, Dec. 2, 1999: 1398-1414; 1444-1508; 1532-1548.
Tobor Deposition Testimony, Dec. 3, 1999: 1652-1653; 1662-1672; 1683-1694.
Kula Deposition Testimony, Apr. 20, 1999: 268-169.
Kula Deposition Testimony, Nov. 16, 1999: 660-675; 680-694; 7-8-755; 774-821.
Kula Deposition Testimony, Nov. 18, 1999: 176-223.
Expert Report of Dr. Rodney S. Badger on Behalf of Medtronic AVE, Inc. (Jan. 31, 2000).
Expert Report of Dr. Joseph Bonn on Behalf of Medtronic AVE, Inc. (Jan. 31, 2000).
Deposition of Dr. Joseph Bonn dated Mar. 14, 2000.
Rebuttal Expert Report of Nigel Buller, B.Sc., M.B., F.R.C.P. (Mar. 2000).
Second Supplemental Rebuttal Expert Report of Nigel Buller, B.Sc., M.B., F.R.C.P. (Aug. 17, 2004).
Rebuttal Expert Report of John M. Collins, PH.D. (Feb. 2000).
Expert Report of David C. Cumberland, M.D. (Jan. 24, 2000).
Expert Report of John T. Goolkasian (Feb. 2000).
Deposition of Richard R. Heuser, M.D. (Sep. 7, 2004).
Deposition of Henry R. Piehler (Sep. 10, 2004).
Deposition of Ronald J. Solar (Mar. 22, 2000).
Deposition of Ronald J. Solar (Mar. 23, 2000).
Deposition of Ronald J. Solar (Apr. 12, 2000).
Expert Report of Dr. Arina Van Breda on Behalf of Medtronic AVE, Inc. (Jan. 31, 2000).
Deposition of Anna Van Breda (Mar. 24, 2000).
Deposition of Arina Van Breda (Aug. 21, 2004).
Expert Report of John F. Witherspoon (Jan. 24, 2000).
Supplemental Expert Report of John F. Witherspoon (Oct. 27, 2000).
Deposition of John F. Witherspoon (Mar. 8, 2000).
Palmaz et al., Article: "Normal and Stenotic Renal Arteries: Experimental Balloon Expandable Intraluminal Stenting", Radiology, Sep. 1987. (AVE 84).
Julio C. Palmaz, Article: "Expandable vascular endoprosthesis." (AVE 132).
Duprat et. al., Article: Flexible Balloon-Expandable Stent for Small Vessels Duprat et. al. Radiology, vol. 162, pp. 276-278, 1987. (AVE 134).
Coons et. al., Article: "Large-Bore, Long Biliary Endoprosthesis (Biliary Stents) for Improved Drainage," Radiology, vol. 148, pp. 89-94, 1983. (AVE 143).
Honickman et al., Article: "Malpositioned Biliary Endoprosthesis, Technical Developments And Instrumentation," vol. 144, No. 2., 1982. (AVE 144).
Harries-Jones, et al., Article: "Repositioning of Biliary Endoprosthesis with Gruntzig Balloon Catheters," AJR, vol. 138, pp. 771-772, 1982. (AVE 153).
Charnsangavej et al., Article "Stenosis of the Vena Cava: Preliminary Assessment of Treatment with Expandable Metallic Stents," Radiology, vol. 161, pp. 295-298, 1986. (AVE 359).
Wallace, M. J. et al., Article "Tracheobronchial Tree: Expandable Metallic Stents Used in Experimental and Clinical Applications," Radiology, vol. 158, pp. 309-312, 1986. (AVE 364).
T. Yoshioka, et al., AIR Article: "Self-Expanding Endovascular Graft: An Experimental Study in Dogs", vol. 151, pp. 673-676, 1988. (AVE 438).
Palmaz, J. C. et al., Article: "Expandable Intraluminal Vascular Graft: A Feasibility Study," Surgery, vol. 99, pp. 199-205, 1986. (AVE 461).
Lawrence et al., Article: "Percutaneous Endovescular Graft: Experimental Evaluation." Radiology, vol. 163, pp. 357-360, 1987. (AVE 671).
Palmaz et al., Article: Expandable Intraluminal Graft: A Preliminary Study, 1 Jan. 17-22, 1985, Radiology, vol. 156, pp. 73-77, 1985. (AVE 1224).
Fallone et al., "Elastic Characteristics of the Self-Expanding Metallic Stents," Investigative Radiology, vol. 23, pp. 370-376, 1988. (AVE 1953).
Palmaz Paper Entitled "Research Project Expandable Vascular Endoprosthesis" May 18, 1983.
Rousseau , et al., Publication: "Percutaneous Vascular Stent: Experimental Studies & Preliminary Clinical Results in Peripheral Arterial Diseases," in Inter. Angio, vol. 6, 153-161, 1987. (AVE 3301).
Rousseau , et al., Publication: "Self-Expanding Endovascular Prostesis: An Experimental Study," Radiology, vol. 164, pp. 709-714, 1987. (AVE 3303).
Wallace, et al., Article: "Tracheobronchial Tree: Expandable Metallic Stents Used in Experimental and Clinical Applications," Radiology, vol. 58, pp. 309-312, 1986. (DBX 2938).
Palmaz et al., Article: "Expandable Intraluminal Graft: A Preliminary Study," Radiology, vol. 156, pp. 73-77, Nov. 17-22, 1985 (DBX 4595).
Program for the 12th Annual Course on Diagnostic Angiography and Interventional Radiology Mar. 23-26, 1987 sponsored by The Society of Cardiovascular and Interventional Radiology (DBX 6235).
Preliminary Motion for Judgment re: Wolff claims 1, 2-8, 10, 15 and 19 (DBX6759).
Palmaz Declaration (DBX 7069).
Letter from Gaterud to Dr. Palmaz dated Jul. 5, 1988 with attached document entitled: "Segmented, balloon-expandable stents." (DBX 7160).
Duprat et al., Article: "Flexible Balloon-Expandable Stent For Small Vessels," Radiology, vol. 168, pp. 276-278, 1987 (PX 82).
Drawing Sent to Bodic on Mar. 17, 1986 (PX 374).
Letter from Dr. Palmaz to R. Bowman enclosing a model of the flexible coronary graft dated Mar. 17, 1986 (PX 337).
Lab Notebook pages dated Jul. 30, 1987 from Rodney Wolff (COR 185596-597) (PX621A).
Charnsangavej, et al., Article: "Stenosis of The Vena Cava Preliminary Assessment of Treatment with expandable Metallic Stents," Radiology, vol. 161, No. 2, pp. 295-298 with attached photographs, 1986. (API 72).
J. Palmaz: The Current Status of Vascular Prostheses, published by SCIR in the Twelfth Annual Course on Diagnostic Angiography And Interventional Radiology Mar. 23-26, 1987. (API 73).
Amendment in Response to Office Action of Oct. 18, 1998 in re: Application of Julio Palmaz S/N 174,246. (API 152).
Article: Wallace, et al., Tracheobronchial Tree: Expandable Metallic Stents Used in Experimental and Clinical Applications Work In Progress, Radiology, vol. 158, pp. 309-312. (API 295).
Reply of Senior Party Schatz To Patentee Wolffs Opposition To The Belated Motion For Judgment Of Applicant Schatz With Regard To Wolff Claims 1, 2-8, 10, 1 1, 13-17, And 19 (COR 186450-455) (API 310).
Brief Of Senior Party Schatz At Final Hearing (API 313).
Letter from Ron Sickles to Ben Tobor dated Feb. 10, 1988 (Exhibit 42).
Letter from R.O. Sickles to Mike Tatlow dated May 12, 1988 (Exhibit 43).
Letter from R. O. Sickles to Richard Schatz dated Jun. 2, 1988 (Exhibit 44).
Letter from Richard Schatz to Raimund Erbel dated Jun. 3, 1988 (Exhibit 45).
Letter from Richard Schatz to Mike Schuler dated Aug. 29, 1991 (Exhibit 48).
Minutes of J&J Stent Project Review Meeting dated Jan. 21, 1988 (Exhibit 7).
Preliminary Motion for Judgment with Regard to Wolff Claims 1, 2-8, 10, 11, 13-17, and 19. (Exhibit 67).
Declaration of Richard A Schatz. (Exhibit 75).
Belated Motion for Judgment with Regard to Wolff Claims 1, 2-8, 10, 1 1, 13-17 and 19. (Schatz-Exhibit 77).
Letter from Dr. Schatz to Mr. Tobor, dated Jun. 3, 1988. (Exhibit 122).
Letter from Dr. Schatz to Mr. Romano, dated Nov. 28, 1988. (Exhibit 131).
Letter from Mr. Sickles to Mr. Tobor, dated Feb. 10, 1988 (Exhibit 145).
Richard A. Schatz, Article titled: "A View of Vascular Stents" Circulation, vol. 79, No. 2, pp. 445-457, 1989. (Exhibit 194).

Senior Party Schatz's reply to Patentee Wolffs Opposition to the Preliminary Motion Of Applicant Schatz for judgment with regard to Wolff Claims 1, 2-8, 10, 1 1, and 13-17. (Exhibit 69).
Wallace, et al., Article: "Tracheobronchial Tree: Expandable Metallic Stents Used in Experimental and Clinical Applications' Work In Progress," Radiology, vol. 158, pp. 309-312, 1986. (Exhibit 165).
Charnsangavej, et al., Article: "Stenosis of The Vena Cava Prelimimnary Assessment of Treatment with expandable Metallic Stents," Radioloby, vol. 161, No. 2, pp. 295-298 with attached photographs, 1986! (Exhibit 167).
David D. Lawrence et al., Publication: Percutaneous Endoyascular Graft: Experimental Evaluation[1], Radiology, pp. 163, 357-360, 1987. (Exhibit 173).
Charles E. Putnam, M.D., Cover and article from "Investigative Radiology", vol. 23. No. 5, May 1988. (Exhibit 177).
Robert N. Berk, Cover and article from "American Journal of Roentology", pp. 673-676, 1988. (Exhibit 178).
Declaration of John S. Kula Under 37 CFR § 1 .672. (Kula-Exhibit 77).
Yoshioka et al., Article: "Self-Expanding Endovascular Graft: An Experimental Study in Dogs" AJR, vol. 151, pp. 673-676, 1988. (PX 100).
Palmaz, et al., Article: Expandable Intraluminal Graft: A Preliminary Study Work in Progress[1], Radiology, vol. 156, No. 1, pp. 73-77, 1985. (PX 101).
Declaration of Richard Schatz Under 37 C.F.R. § 1.672. (PX 106).
Charnsangavej et al., Article: "Stenosis of the Vena Cave: Preliminary Assessment of Treatment with Expandable Metallic Stents," Radiology, vol. 161, pp. 295-298, 1986. (PX 143).
Wallace, et al., Article: Tracheobronchial Tree: Expandable Metallic Stents Used in Experimental and Clinical Applications Work in Progress[1], Radiology, vol. 158, pp. 309-312, 1986. (PX 144).
Gina Kolata, News Article: NY Times, "Devices That Opens Clogged Arteries Gets a Falling Grade in a New Study", pp. 16-18, Jan. 3, 1991. (PX 186).
Duprat, et al., Article: "Flexible Balloon- Expanded Stent for Small Vessels Work in Progress[1]", Radiology, vol. 162, pp. 276-278, 1987. (PX 207).
Letter from Palmaz to Bowman dated Mar. 17, 1986. (PX 350).
Memo re: Minutes of Stent Project Review- San Antonia- Mar. 15, 1988. (PX 651).
Kuntz, et al., Article: Clinical Cardiology Frontiers: "Defining Coronary Restenosis, Newer Clinical and Angiographic Paradigms", Circulation, Sep. 1993, vol. 88, No. 3, pp. 1310-1323. (PX 854).
Belated Motion for Judgment with regard to Wolff Claims1, 2-8, 10, 11, 13-17, and 19. (PX 1410).
Drawing of Spiral Stent (sent to Bodic Mar. 17, 1986). (PX2933).
Wright et al., Article: "Percutaneous Endovascular Stents: An Experimental Evaluation," Radiology, vol. 156, pp. 69-72, 1985. (PX 3093).
Charnsangavej et al., Article: "A New Expandable Metallic Stent for Dilation of Stenotic Tubular Structures: Experimental and Clinical Evaluation," Houston Medical Journal, vol. 3, pp. 41-51, Jun. 1987. (PX 3207).
In re Application of Wiktor, Appln. No. 69,636, Response to Office Action dated Mar. 17, 1988. (PX3236).
Transmittal Letter of Response to First Office Action in '417 patent. (PX 3993).
Letter from B. Tobor to R. Schatz dated Jul. 23, 1991. (PX 3996).
Mullins et al., Article: "Implication of balloon-expandable intravascular grafts by catherization in pulmonary arteries and systemic veins," Circulation, vol. 77, No. 1, pp. 188-189, 1988. (PX4049).
Schatz et al., Article: "Intravascular Stents for Angioplasty," Cardio, 1997. (PX 4050).
Schatz et al., Article: "New Technology in Angioplasty Balloon-Expandable Intravascular Stents, New Developments in Medicine," vol. 2, No. 2 pp. 59-75, 1987. (PX4051).
Richard A. Schatz, Article: "Introduction to Intravascular Stents," Cardiology Clinics, vol. 6, No. 3, pp. 357-372, 1988. (PX 4052).
Richard A. Schatz, Article: "A View of Vascular Stents," Circulation, vol. 79, No. 2, pp. 445-457, 1989. (PX4053).
Wang et al., Article: "An Update on Coronary Stents," Cardio, pp. 177-186, 1992. (PX 4054).
Richard A. Schatz, Article: "New Technology in Angioplasty: Balloon-Expandable Starts," Medicamundi, vol. 33, No. 3, pp. 1 12-1 26, 1988. (PX 4055).
Letter from Tobor to Schatz dated Sep. 29, 1988. (PX 1395).
Verified Statement of Facts by Unnamed Inventor R.A. Schatz document filed in U. S. Patent and Trademark Office on Sep. 8, 1989. (PX 3677).
Declaration of John S. Kula Under 37 CFR § 1.672 (Exhibit 329).
Letter to Mike Schular from R.A. Schatz dated Aug. 29, 1991. (Exhibit 402).
Articulated, Balloon-Expandable Stents, (DBX 7159).
J. Rosch et al., Experimental Intrahepatic Portacaval Anastomosis: Use of Expandable Gianturco Stents, Radiology, vol. 162, pp. 481-485, 1987.
J. Rosch et al., Modified Gianturco Expandable Wire Stents In Experimental and Clinical Use, Ann Radiol, vol. 31, No. 2, pp. 100-103, 1987.
J. Rosch et al., Gianturco Expandable Stents In the Treatment of Superior Vena Cava Syndrome Recurring After Vena Cava Syndrome Recurring After Maximum-Tolerance Radiation, Cancer, vol. 60, pp. 1243-1246, 1987.
I.E. Gordon, Structures or Why Things Don't Fall Down, Penguin Books, pp. 45-59, 132-148,210-244,377-383.
Maass et al., Radiological Follow-up of Transluminally Inserted Vascular Endoprostheses: An Experimental Study Using Expanding Spirals, Radiology, vol. 152, pp. 659-663, 1984.
Argument submitted re EP 861 15473 dated Jan. 20, 1995. (AVE 2478).
Verified Statement of Facts by Julio C. Palmaz dated Aug. 4, 1989. (PX 3662).
Papanicolaou et al., Insertion of a Biliary Endoprosthesis Using A Balloon Dilatation Catheter, Gastrointest Radiology, vol. 10, pp. 394-396, 1985.
Palmaz et al., Atherosclerotic Rabbit Aortas: Expandable Intraluminal Grafting, Radiology, vol. 168, pp. 723-726, 1986.
Palmaz, The Current Status of Vascular Prostheses; Rosch et al., Gianturco, Expandable Stents in Experimental and Clinical Use, SCIVR, pp. 1 18-124, 1987.
Rosch et al., Abstract: Modified Gianturco Expandable Wire Stents in Experimental and Clinical Use, CIRSE, Porto Cervo, Sardinia, May 25-29, 1987.
Rosch et al., Gianturco Expandable Wire Stents in the Treatment of Superior Vena Cava Syndrome Recurring After Maximum-Tolerance Radiation, Cancer, vol. 60, pp. 1243-1246, 1987.
Mirich et al., Percutaneously Placed Endovascular Grafts for Aortic Aneurysms: Feasibility Study, Radiology, vol. 170, pp. 1033-1037, 1989.
Dotter, Transluminally-placed Coilspring Endarterial Tube Grafts, Investigative Radiology, vol. 4, Sep.-Oct., pp. 329-332, 1969.
Palmaz et al., Abstract: Expandable Intraluminal Graft: A Preliminary Study, Radiology, vol. 153 (P), Nov. 1983: 70th Scientific Assembly and Annual Meeting.
Cragg et al, Nonsurgical Placement of Arterial Endoprostheses: A New Technique Using Nitinol Wire, Radiology, vol. 147, pp. 261-263, Apr. 1983.
J. Rosch et al., Gianturco Expandable Stents in Experimental and Clinical Use, Program: "Twelfth Annual Course on Diagnostic Angiography and Interventional Radiology" (Society of Cardiovascular and Interventional Radiology, Pittsburgh, PA), Mar. 23-26, 1987 (the second Monofilament Article).
Uchida et al., Modifications of Gianturco Expandable Wire Stents, AIR, vol. 150, pp. 1185-1187, 1988.
Palmaz, Balloon-Expandable Intravascular Stent, AJR, vol. 1510, pp. 1263-1269.
Cordis Corporation v. *Advanced Cardiovascular Systems, Inc.*, Guidant Corporation, Arterial Vascular Engineering, Inc., Boston Scientific Corporation and SCMED Life Systems, Inc., Plaintiffs Complaint, Oct. 23, 1997 (Case No. 97-550-SLR).
Arterial Vascular Engineering, Inc. v. *Cordis Corporation*, Johnson & Johnson and Expandable-Grafts Partnership, Plaintiffs First Amended Complaint for Declaratory Relief of Patent Validity,

Unenforceability, Noninfiingement, and for Antitrust Violations, Jan. 27, 1998 (Civil Action No. 97-700).
Arterial Vascular Engineering, Inc. v. *Cordis Corporation*, Johnson & Johnson and Expandable-Grafts Partnership, Cordis Corporation and Johnson & Johnson's Answer and Counterclaim, Feb. 27, 1998 (Civil Action No. 97-700-SLR).
Arterial Vascular Engineering, Inc. v. *Cordis Corporation*, Johnson & Johnson and Expandable-Grafts Partnership, Expandable-Graft Partnership's Answer, Feb. 27, 1998 (Civil Action No. 97-700-SLR).
Arterial Vascular Engineering, Inc. v. *Cordis Corporation*, Johnson & Johnson and Expandable-Grafts Partnership, Reply of Plaintiff Arterial Vascular Engineering, Inc. To Counterclaims of Defendant Cordis Corporation, Mar. 31, 1998 (Civil Action No. 97-700-SLR).
Arterial Vascular Engineering, Inc. v. *Cordis Corporation*, Johnson & Johnson and Expandable-Grafts Partnership, Reply of Plaintiff Arterial Vascular Engineering, Inc. To Counterclaims of Defendant Expandable Grafts Partnership, Mar. 31, 1998 (Civil Action No. 97-700-SLR).
Cordis Corporation v. *Advanced Cardiovascular Systems, Inc. and Guidant Corporation*, Cordis Corporation's Motion for a Preliminary Injunction, Oct. 8, 1997 (Civil Action No. 97-550).
Cordis Corporation v. *Advanced Cardiovascular Systems, Inc.*, Guidant Corporation Arterial Vascular Engineering, Inc., Boston Scientific Corporation and SCIJVIED, Inc., Cordis's Motion for Preliminary Injunction Against Arterial Vascular Engineering, Inc., Dec. 29, 1997 (Case No. 97-550-SLR).
Deposition of R. Schatz, M.D. in *Cordis Corporation* v. *Advanced Cardiovascular Systems, Inc.*, taken on Jan. 8, 1998 (Civil Action No. 97-550 SLR).
Deposition of Lee P. Bendel in *Cordis Corporation* v. *Advanced Cardiovascular Systems, Inc.*, taken on Jan. 22, 1998 (Civil Action No. 97-550 SLR).
Deposition of Julio Cesar Palmaz in *Cordis Corporation* v. *Advanced Cardiovascular Systems, Inc.*, taken on Dec. 29, 1997 (Civil Action No. 97-550 SLR).
Deposition of Richard A. Bowman in *Cordis Corporation* v. *Advanced Cardiovascular Systems, Inc.*, taken on Jan. 9, 1998 (Civil Action No. 97-550 SLR).
Deposition of Gary Schneiderman in *Cordis Corporation* v. *Advanced Cardiovascular Systems, Inc.*, taken on Jan. 16, 1998 (Civil Action No. 97-550 SLR).
Deposition of David Pearle, M.D. in *Cordis Corporation* v. *Advanced Cardiovascular Systems, Inc.*, taken on Jul. 10, 1998 (Civil Action No. 97-550 SLR).
Preliminary Injunction hearing testimony taken on Feb. 9-13, 1998 (Civil Action No. 97-550 SLR).
Cordis Corporation v. *Advanced Cardiovascular Systems, Inc., et al.*, (Civil Action No. 97-550 SLR) and *Cordis Corporation* v. *Advanced Cardiovascular Systems, Inc. Et al.* (Civil Action No. 98-65-SLR), Opening Post Hearing Brief of Plaintiff Cordis Corporation in Support of Motion for Preliminary Injunction, Mar. 6, 1998 (Portions relevant to patent claim construction and patent validity issues).
Cordis Corporation and Expandable Grafts Partnership v. *Advanced Cardiovascular Systems, Inc. et al.*, Post-Hearing Reply Brief of Plaintiff Cordis Corporation in Support of Its Motion for Preliminary Injunction, Apr. 10, 1998 (Case No. 97-550 SLR) (Portions relevant to patent validity issues).
Cordis Corporation and Expandable Grafts Partnership v. *Advanced Cardiovascular Systems, Inc. et al.*, Plaintiffs Motion for a Preliminary Injunction Against Boston Scientific Corporation and SCLMED Life Systems, Inc. And Memorandum in Support, Apr. 13, 1998 (Case No. 97-550-SLR).
Cordis Corporation and Expandable Grafts Partnership v. *Advanced Cardiovascular Systems, Inc., et al.*, Judge Robinson's Order Denying Plaintiffs Motion for a Preliminary Injunction, Jul. 17, 1998 (Civil Action No. 97-550 SLR).
Cordis Corporation and Expandable Grafts Partnership v. *Advanced Cardiovascular Systems, Inc., et al.*, Defendant Boston Scientific Corporation and SCTMED Life Systems, Inc.'s Motion for Summary Judgment of Invalidity of U.S. Appl. No. 5,102,417, filed Aug. 27, 1998 (Civil Action No. 97-550- SLR).
Boston Scientific Limited, et al. v. *Expandable Grafts Partnership*, Plaintiffs' Statement of Claim, Mar. 13, 1997 (UK Action No. 1493).
Boston Scientific Limited, et al. v. *Expandable Grafts Partnership*, Defendant's Amended Defense and Counterclaim, Aug. 14, 1997 (UK Action No. 1493).
Boston Scientific Limited, et al. v. *Expandable Grafts Partnership*, Petition for Revocation, Mar. 13, 1997 (UK Action No. 1497).
Boston Scientific Limited, et al. v. *Expandable Grafts Partnership*, Particulars of Objections, Mar. 13, 1997 (UK Action No. 1497).
Boston Scientific Limited, et al. v. *Expandable Grafts Partnership and Boston Scientific Limted et al.*, v. *Julio C. Palmaz*, Boston's Skeleton Argument (UK Action Nos. 1493, 1495, 1496, and 1497).
Boston Scientific Limited, et al. v. *Julio C. Palmaz and Expandable Grafts Partnership*, Skeleton Argument of Palmaz/EGP, Mar. 19, 1998 (UK Action Nos. 1493, 1495, 1496 and 1497).
Boston Scientific Limited, et al. v. *Julio C. Palmaz and Expandable Grafts Partnership*, EGP's Final Submissions, Apr. 2, 1998 (UK Action Nos. 1493, 1495, 1496 and 1497).
Boston Scientific Limited, et al. v. *Julio C. Palmaz and Expandable Grafts Partnership*, Judgment, Jun. 26, 1998 (UK Action Nos. 1493, 1495, 1496 and 1497).
Rosch, Modified Gianturco Expandable Wire Stents in Experimental and Clinical Use, CJJR.SE 1987 Presentation: see Witness Statement of Josef Rosch from U.K. Proceeding.
Statement of Claim by Boston Scientific et al. against Expandable Grafts Partnership et al., in *EPG et al.*, v. *Boston Scientific et al.* in Netherlands (Mar. 13, 1997).
Motion for Joinder of Actions, Change of Claim and Statement of Claim filed by Expandable Grafts Partnership et al. in *EPG et al.* v. *Boston Scientific et al.* In Netherlands (Apr. 22, 1997).
Opinion of K.J. Merman filed *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Aug. 29, 1997).
Expert report of Dr. Nigel Buller in *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Aug. 28, 1997).
Expert report of Lee P. Bendel in *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Aug. 28, 1997).
Memorandum of Oral Pleading in *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Sep. 12, 1997).
Plea Notes of P. A.M. in *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Mar. 10, 1998).
Decision of Court of Appeals in *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Apr. 23, 1998).
Translation of Nullity Action Against EPO 0 364 787 by Biotronik in Germany.
Translation of Nullity Action Against EPO 0 335 341 by Biotronik in Germany.
Translation of EPG Response to Nullity Action Against EP 0 364 787 by Biotronik in Germany.
Translation of EPG Response to Nullity Action EP 0 335 341 by Biotronik in Germany.
Nullity Suit Against EP-B1-0 335 341 Brought by Boston Scientific in Germany.
Translation of Opposition filed by Terumo Corp. Against Japan Patent No. 2680901.
Translation of Decision on Opposition Against Japan Patent No. 2680901.
Memorandum Order of the Court dated Sep. 7, 2000, concerning disputed claim construction.
Translation of Judgment in Nullity Action Against EP 0 364 787 by Biotronik in Germany.
Translation of Judgment in Nullity Action Against EP 0 335 341 by Biotronik in Germany.
Trial transcript from Mar. 17, 2005 at 171-172, 191-192.
Trial transcript from Mar. 18, 2005 at 282-285, 325-327, 349-351.
Trial transcript from Mar. 21, 2005 at 721-726.
Trial transcript from Mar. 24, 2005 at 1387.
Trial transcript from Jul. 26, 2005.
BSC's Opening Brief in Support of Its Motion for Judgment as a Matter of Law or, in the Alternative, for a New Trial, dated Mar. 16, 2001.

Cordis' Answering Brief in Opposition to BSC's Motion for JMOL or a New Trial on the Palmaz '762 Patent and the Schatz '332 Patents, dated Apr. 17, 2001.
BSC's Reply Brief in Support of Its Motion for Judgment as a Matter of Law or, in the Alternative, for a New Trial, dated May 11, 2001.
J. Rosch et al., Abstract, Expandable Gianturco-Type Wire Stents in Experimental Intrahepatic Portacaval Shunts, Program: "72nd Scientific Assembly and Annual Meeting of the Radiological Society of North America", Nov. 30-Dec. 5, 1986, Radiology, vol. 161, pp. 40-41, 1986.
Cordis Corporation v. *Boston Scientific*, Order Dated Mar. 27, 2006 (97-550-SLR).
Cordis Corporation v. *Boston Scientific*, Judgment in a Civil Case Dated Mar. 27, 2006 (97-550-SLR).
Cordis Corporation v. *Boston Scientific*, Memorandum Opinion Dated Mar. 27, 2006 (97-550-SLR).
Cordis Corporation v. *Boston Scientific*, Order Dated Mar. 27, 2006 (97-550-SLR).
Cordis Corporation and Expandable Grafts Partnership v. *Advanced Cardiovascular Systems, Inc., Guidant Corporation, Arterial Vascular Engineering, Inc., Boston Scientific Corporation and SCIMED Life Systems, Inc.*, Answer and Counterclaims of Defendant Advanced Cardiovascular Systems, Inc., Apr. 8, 1998 (Case No. 97-550-SLR).
Boston Scientific Limited et al. v. *Expandable Grafts Partnership and Boston Scientific Limited et al.* v. *Julio C. Palmaz*, Boston's Closing Submissions (UK Action Nos. 1493, 1495, 1496 and 1497).
Cordis Corporation v. *Advanced Cardiovascular Systems, Inc., Guidant Corporation, Arterial Vascular Engineering, Inc., Boston Scientific Corporation and SCIMED Life Systems, Inc.*, Defendants' Answer, Nov. 12, 1997 (Case No. 97-550-SLR).
Statement of Rejoinder in the Action on the Merits, Also Including an Amendment of Defendant's Final Position in the Principal Action, as Well as the Provisional Statement of Rejoinder in the Action on the Counterclaim in *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Feb. 10, 1998).
Statement of Answer in the Ancillary Appeal in *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Mar. 10, 1998).
Appeal filed by Expandable Grafts Partnership et al. in *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Nov. 12, 1997).
Title filed by Boston Scientific et al. in *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Jan. 22, 1998).
Deposition of Richard Schatz, M.D. in *Cordis Corporation* v. *Advanced Cardiovascular Systems, Inc.* taken on Jul. 14, 1998 (Civil Action No. 97-550-SLR).
Jury Verdict form from the *Cordis Corporation et al* v. *Boston Scientific Corporation, et al* liability trial, undated.
Trial testimony transcripts from the *Cordis Corporation et al.* v. *Boston Scientific Corporation et al.* liability trial dated Nov. 21, Nov. 27-Dec. 1, Dec. 4-8 and Dec. 11, 2000.
Boston Scientific SCIMED, Inc. and Boston Scientific Corporation v. *Cordis Corporation and Johnson and Johnson, Inc.*, Opening Expert Report of Stephen R. Hanson, Ph.D. (Civil Action No. 03-283-SLR).
Boston Scientific SCIMED, Inc. and Boston Scientific Corporation v. *Cordis Corporation and Johnson and Johnson, Inc.*, Opening Expert Report of Robson F. Storey, Ph.D. (Civil Action No. 03-283-SLR).
Boston Scientific SCIMED, Inc. and Boston Scientific Corporation v. *Cordis Corporation and Johnson and Johnson, Inc.*, Rebuttal Expert Report of Kinam Park, Ph.D. (Civil Action No. 03-283-SLR).
Cordis Corporation v. *Boston Scientific Corporation and SCIMED Life Systems, Inc.* (C.A. No. 03-027-SLR) and *Boston Scientific SCIMED, Inc., and Boston Scientific Corporation* v. *Cordis Corporation and Johnson and Johnson, Inc.* (C.A. No. 03-283-SLR) Combined Post-Hearing Brief In Support Of Cordis Corporation's Motion For Preliminary Injunction in C.A. No. 03-027-SLR, And In Opposition to Plaintiffs' Motion For Preliminary Injunction in C.A. No. 03-283-SLR.
Cordis Corporation v. *Boston Scientific Corporation and SCIMED Life Systems, Inc.* (C.A. No. 03-027-SLR) *Boston Scientific SCIMED, Inc., and Boston Scientific Corporation* v. *Cordis Corporation and Johnson and Johnson, Inc.* (C.A. No. 03-283-SLR), Boston Scientific's Opening Post-Hearing Brief.
Wu et al., Silicone-covered self-expanding metallic stents for the palliation of malignant esophageal obstruction and esophagorespiratory fistulas: experience in 32 patients and a review of the literature, *Gastrointestinal Endoscopy*, 1994, pp. 22-33, vol. 40, No. 1, Portland Oregon.
Binmoeller, et al., Silicone-Covered Expandable Metallic Stents in the Esophagus: An Experimental Study, Endoscopy, 1992, pp. 416-420, vol. 24, Georg Thieme Verlag Stuttgart New York.
Boston Scientific SCIMED, Inc., and Boston Scientific Corporation v. *Cordis Corporation and Johnson and Johnson, Inc.*, Answering Memorandum in Opposition to Plaintiffs Motion for a Preliminary Injunction and Appendix thereto (Civil Action No. 03-283-SLR).
Boston Scientific SCIMED, Inc., and Boston Scientific Corporation v. *Cordis Corporation and Johnson and Johnson, Inc.*, Plaintiff s Reply Brief in Support of Their Motion for Preliminary Injunction.
Rhine, Polymers for Sustained Macromolecule Release: Procedures to Fabricate Reproducible Delivery Systems and Control Release Kinetics, *Journal of Pharmaceutical Sciences*, 1 980, pp. 265-270, vol. 69, No. 3.
Langer et al., Controlled Release of Macromolecules From Polymers, *Biomedical Polymers Polymeric Materials and Pharmaceuticals for Biomedical Use*, 1980, pp. 112-137, Academic Press, Inc., New York, NY.
Langer et al., Applications of Polymeric Delivery Systems for Macromolecules and Factors Controlling Release Kinetics.
Rhine et al., A Method to Achieve Zero-Order Release Kinetics From Polymer Matric Drug Delivery Systems, pp. 67-72.
Langer et al., Polymers for the Sustained Release of Macromolecules: Controlled and Magnetically Modulated Systems, *Better Therapy With Existing Drugs: New Uses and Delivery Systems*; 1981, pp. 179-216, Merck Sharp & Dohme International, Rahway, NJ.
Hsieh, et al., Zero-Order Controlled-Release Polymer Matrices for Micro-and-Macromolecules, *Journal of Pharmaceutical Sciences*, 1983 pp. 17-22, vol. 72, No. 1.
Brown et al., In Vivo and In Vitro Release of Macromolecules from Polymeric Drug Delivery Systems, *Journal of Pharmaceutical Sciences*, 1983, pp. 1181-1185, vol. 72, No. 10.
Langer, Implantable Controlled Release Systems, *Pharmac. Ther.*, 1983, pp. 35-51, vol. 21, printed in Great Britain.
Kost et al., Controlled Release of Bioactive Agents, *Trends in Biotechnology*, 1984, pp. 47-51, vol. 2, No. 2, Elsevier BV Amsterdam.
Bawa et al., An Explanation for the Controlled Release of Macromolecules from Polymers, *Journal of Controlled Release*, 1985, pp. 259-267, vol. 1 Elsevier Science BV Amsterdam.
Leong et al., Polymeric controlled drug delivery, 1987, pp. 199-233, vol. 1/3, Elsevier Science Publishers BV Amsterdam.
Langer, Polymeric Delivery Systems, *Targeting of Drugs 2 Optimization Strategies*, 1989, pp. 165-174, Plenum Press, New York and London.
Langer, Biomaterials in Controlled Drug Delivery; New Persectives from Biotechnological Advances; *Pharmaceutical Technology*, 1989, pp. 18, 23-24, 26, 28, 30.
Langer, Controlled Release Systems, pp. 115-124.
Laurencin et al., Polymeric Controlled Release Systems: New Methods for Drug Delivery, *Clinics in Laboratory Medicine*, 1987, pp. 301-323, vol. 7, No. 2, WB Saunders Company, Philadelphia.
Langer, Biopolymers in Controlled Release Systems, *Polymeric Biomaterials*, pp. 161-169.
Tsong-Pin Hsu et al., Polymers for the Controlled Release of Macromolecules: Effect of Molecular Weight of Ethylene-vinyl Acetate Copolymer, *Journal of Biomedical Materials Research*, 1985, pp. 445-460, vol. 19.
Langer, Polymers and Drug Delivery Systems, *Long-Acting Contraceptive Delivery Systems*, 1983, pp. 23-32, Harper & Row, Philadelphia, PA.
Langer, New Drug Delivery Systems: What the Clinician Can Expect, *Drug Therapy*, 1983, pp. 217-231.

Langer, et al., Chemical and Physical Structure of Polymers as Carriers for Controlled Release of Bioactive Agents: A Review, *Rev. Macromol. Chem. Phys.*, 1983, pp. 61-126.
Langer, Polymeric Delivery Systems for Controlled Drug Release, *Chem. Eng. Commun.* 1980, pp. 1-48-vol. 6, Gordon and Breach Science Publishers, Inc. USA.
Langer, et al., Biocompatibility of Polymeric Delivery Systems for Macomolecules, *Journal of Biomedical Materials Research*, 1981, pp. 267-277, vol. 15.
Langer, Controlled Release: A New Approach to Drug Delivery, *Technology Review*, 1981, pp. 26-34.
Langer, et al., Sustained Release of Macromolecules from Polymers, *Polymeric Delivery Systems*, pp. 175-176, Gordon and Breach Science Publishers, New York.
Langer, Polymers for the Sustained Release of Proteins and other Macromolecules, *Nature*, 1976, pp. 797, 263, 799-800, vol. 263, No. 5580.
Baker, et al., Controlled Release: Mechanisms and Rates (1974).
Hanson, et al., In Vivo Evaluation of Artificial Surfaces with a Nonhum Primate Model of Arterial Thrombosis,/ *Lab Clin. Med.*, Feb. 1980, pp. 289-304.
Baker, Controlled Release of Biologically Active Agents (1987) pp. 1-275.
Cordis Corporation v. *Boston Scientific Corporation* (CA. No. 03-27-SLR) and *Boston Scientific Scimed, Inc.*, v. *Cordis Corporation and Johnson & Johnson, Incorporated* (CA. No. 03-283-SLR) Hearing Transcripts for Jul. 21, 2003, Jul. 22, 2003, Jul. 23, 2003.
Cordis Corporation v. *Boston Scientific Corporation et al.* (CA. No. 03-027-SLR), and *Boston Scientific Scimed, Inc. et al.* v. *Cordis Corporation et al.* (CA. No. 03-283-SLR), Boston Scientific's Post-Hearing Reply Brief and Exhibits Thereto, Sep. 12, 2003.
Cordis Corporation v. *Boston Scientific Corporation et al.* (CA. No. 03-027-SLR), and *Boston Scientific Scimed, Inc. et al.* v. *Cordis Corporation et al.* (CA. 03-283-SLR), Memorandum Order, Nov. 21, 2003.
Cordis Corporation v. *Boston Scientific Corporation et al.* (CA. No. 03-027-SLR), and *Boston Scientific Scimed, Inc. et al.* v. *Cordis Corporation et al* (CA. No. 03-283-SLR), Deposition Transcript of Julio C. Palmaz.
Plea Notes in *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Sep. 12, 1997).
Provisional Judgment *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Oct. 29, 1997).
Trial testimony transcripts from the *Cordis Corporation et al.* v. *Medtronic AVE Inc., et al.* liability trial dated Nov. 6-9, 13-17 and 20-21, 2000.
Jury verdict form from the *Cordis Corporation et al.* v. *Medtronic AVE, Inc. et al.* liability trial.
Hearing testimony trascript from the consolidated *Cordis Corporation et al.* v. *Medtronic AVE, Inc. et al.* and Boston Scientific Corporation et al. inequitable conduct hearing dated Feb. 7-9 and 12, 2001.
Cordis Corporation v. *Metronic Ave., Inc. et al*, OPINION, 97-550-SLR, dated Mar. 28, 2002.
Cordis Corporation v. *Advanced Cardiovascular Systems, Inc. et al.* (CA. No. 97-550-SLR), *Metronic AVE, Inc.* v. *Cordis Corporation et al.* (CA. No. 97-700-SLR), *Boston Scientific Corporation* v. *Athicon, Inc. etal.* (CA. No. 98-19-SLR), Expert Report of John T. Goolkasian, Esq.
Cordis Corporation v. *Advanced Cardiovascular Systems, Inc. et al.* (CA. No. 97-550-SLR), *Medtronic A VE, Inc.* v. *Cordis Corporation et al* (CA. No. 97-700-SLR), *Boston Scientific Corporation* v. *Athicon, Inc. et al* (CA. 98-19-SLR), Expert Report to John F. Witherspoon.

* cited by examiner

FIG. 1

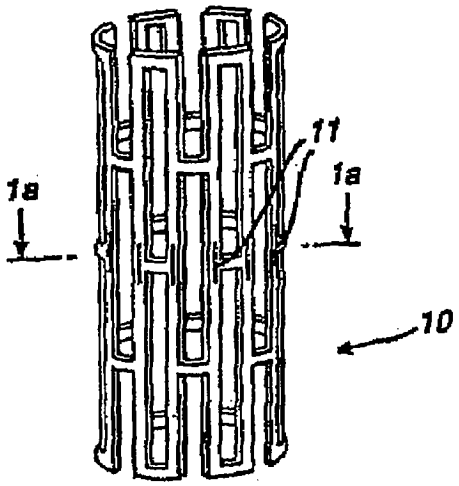


FIG. 1a

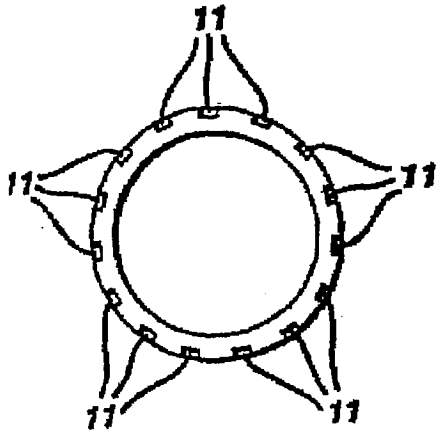


FIG. 2a

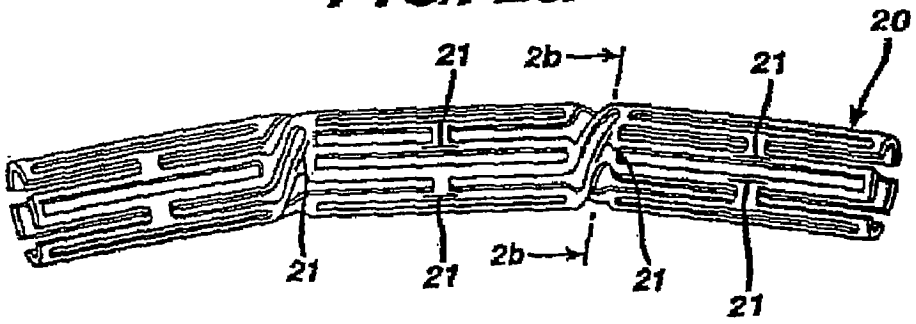


FIG. 2b

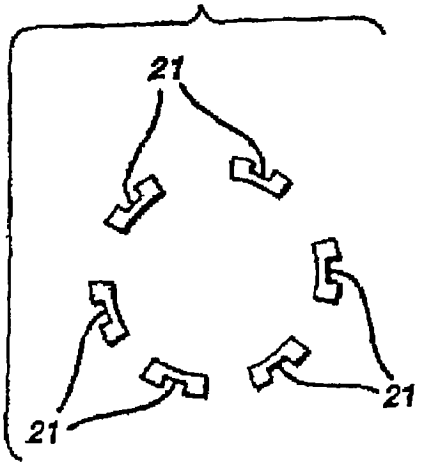


FIG. 3a

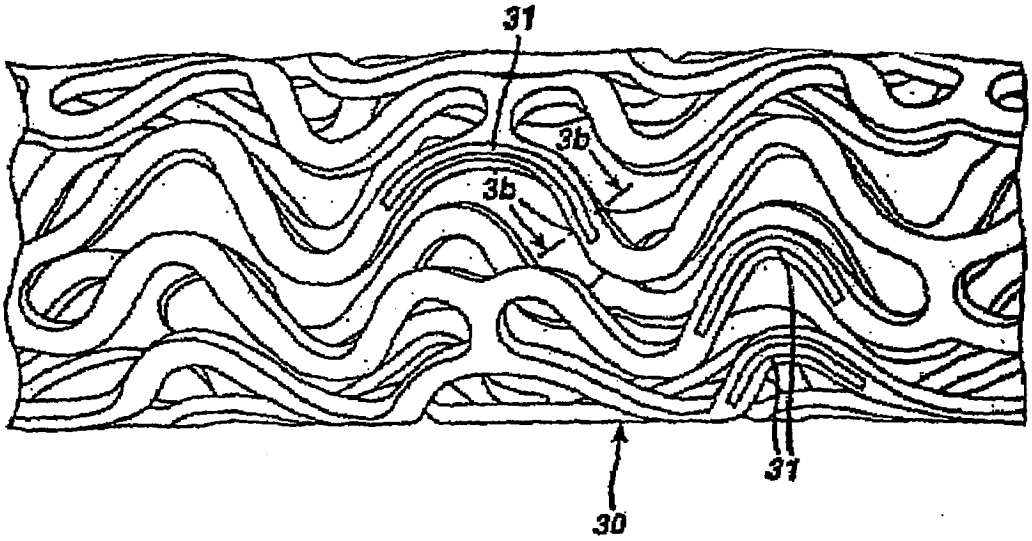


FIG. 3b

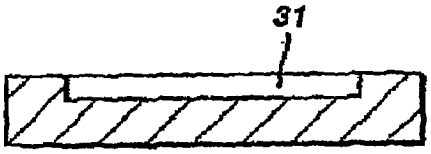
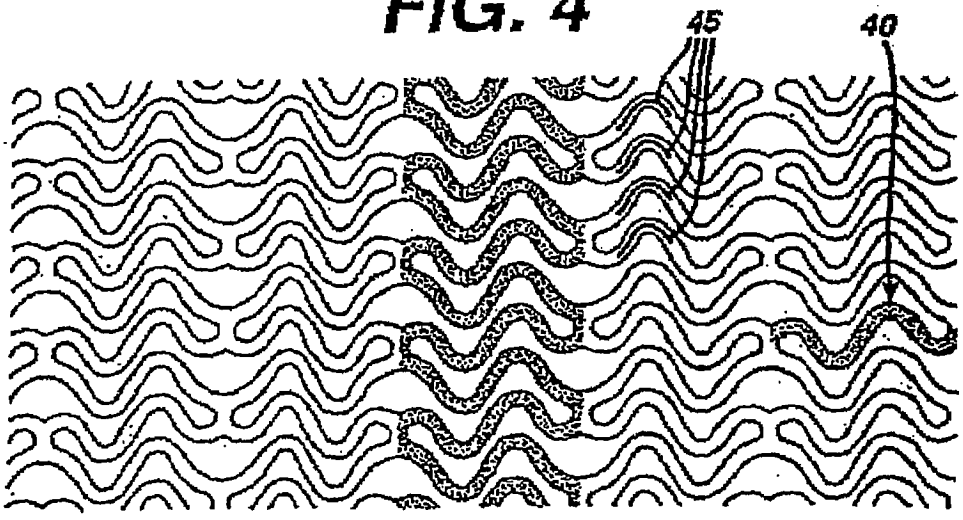


FIG. 4



LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of Ser. No. 10/951,385, filed Sep. 28, 2004, now pending, which in turn is a continuation of Ser. No. 10/408,328, filed Apr. 7, 2003, now issued as U.S. Pat. No. 6,808,536, which in turn is a continuation of application Ser. No. 09/874,117, filed Jun. 4, 2001, now issued as U.S. Pat. No. 6,585,764, which is a continuation of application Ser. No. 09/061,568, filed Apr. 16, 1998, now issued as U.S. Pat. No. 6,273,913, which in turn claims benefit of provisional application Ser. No. 60/044,692, filed Apr. 18, 1997. The disclosures of these prior applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

BACKGROUND OF THE INVENTION

Re-narrowing (restenosis) of an artherosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10–50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft. While the exact hormonal and cellular processes promoting restenosis are still being determined, our present understanding is that the process of PTCA, besides opening the artherosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC). In response to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3–6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow.

Several recent experimental approaches to preventing SMC proliferation have shown promise althrough the mechanisms for most agents employed are still unclear. Heparin is the best known and characterized agent causing inhibition of SMC proliferation both in vitro and in animal models of balloon angioplasty-mediated injury. The mechanism of SMC inhibition with heparin is still not known but may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes c-fos and c-myc, 2) reduced cellular production of tissue plasminogen activator; are 3) binding and dequestration of growth regulatory factors such as fibrovalent growth factor (FGF).

Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers, angiotensin converting enzyme inhibitors (captopril, cilazapril), cyclosporin A, trapidil (an antianginal, antiplatelet agent), terbinafine (antifungal), colchicine and taxol (antitubulin antiproliferatives), and c-myc and c-myb antinsense oligonucleotides.

Additionally, a goat antibody to the SMC mitogen platelet derived growth factor (PDGF) has been shown to be effective in reducing myointimal thickening in a rat model of balloon angioplasty injury, thereby implicating PDGF directly in the etiology of restenosis. Thus, while no therapy has as yet proven successful clinically in preventing restenosis after angioplasty, the in vivo experimental success of several agents known to inhibit SMC growth suggests that these agents as a class have the capacity to prevent clinical restenosis and deserve careful evaluation in humans.

Coronary heart disease is the major cause of death in men over the age of 40 and in women over the age of fifty in the western world. Most coronary artery-related deaths are due to atherosclerosis. Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500,000–600,000 deaths in the United States annually. To arrest the disease process and prevent the more advanced disease states in which the cardiac muscle itself is compromised, direct intervention has been employed via percutaneous transiuminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) PTCA is a procedure in which a small balloon-tipped catheter is passed down a narrowed coronary artery and then expanded to re-open the artery. It is currently performed in approximately 250,000–300,000 patients each year. The major advantage of this therapy is that patients in which the procedure is successful need not undergo the more invasive surgical procedure of coronary artery bypass graft. A major difficulty with PTCA is the problem of post-angioplasty closure of the vessel, both immediately after PTCA (acute reocclusion) and in the long term (restenosis).

The mechanism of acute reocclusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus. Recently, intravascular stents have been examined as a means of preventing acute reclosure after PTCA.

Restenosis (chronic reclosure) after angioplasty is a more gradual process than acute reocclusion: 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty. While the exact mechanism for restenosis is still under active investigation, the general aspects of the restenosis process have been identified.

In the normal arterial will, smooth muscle cells (SMC) proliferate at a low rate (<0.1%/day; ref). SMC in vessel wall exists in a *contractile* phenotype characterized by 80–90% of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, golgi bodies, and free ribosomes are few and located in the perinuclear region. Extracellular matrix surrounds SMC and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining SMC in the contractile phenotypic state.

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the arterial wall become injured. Cell derived growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF),

etc. released from platelets (i.e., PDGF) adhering to the damaged arterial luminal surface, invading macrophages and/or leukocytes, or directly from SMC (i.e., BFGF) provoke a proliferation and migratory response in medial SMC. These cells undergo a phenotypic change from the contractile phenotype to a synthetic phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum, golgi and free ribosomes. Proliferation/migration usually begins within 1–2 days post-injury and peaks at 2 days in the media, rapidly declining thereafter (Campbell et al., In: Vascular Smooth Muscle Cells in Culture, Campbell, J. H. and Campbell, G. R., Eds, CRC Press, Boca.Ratioh, 1987, pp. 39–55); Clowes, A. W. and Schwartz, S. M., Circ. Res. 56:139–145, 1985).

Finally, daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate. Proliferation and migration continues until the damaged luminal endothelial layer regenerates at which time proliferation ceases within the intima, usually within 7–14 days postinjury. The remaining increase in intimal thickening which occurs over the next 3–6 months is due to an increase in extracellular matrix rather than cell number. Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response. (Liu et al., Circulation, 79:1374–1387, 1989).

Patients with symptomatic reocclusion require either repeat PTCA or CABG. Because 30–50% of patients undergoing PTCA will experience restenosis, restenosis has clearly limited the success of PTCA as a therapeutic approach to coronary artery disease. Because SMC proliferation and migration are intimately involved with the pathophysiological response to arterial injury, prevention of SMC proliferation and migration represents a target for pharmacological intervention in the prevention of restenosis.

SUMMARY OF THE INVENTION

Novel Features and Applications to Stent Technology Currently, attempts to improve the clinical performance of stents have involved some variation of either applying a coating to the metal, attaching a covering or membrane, or embedding material on the surface via ion bombardment. A stent designed to include reservoirs is a new approach which offers several important advantages over existing technologies.

Local Drug Delivery from a Stent to Inhibit Restenosis

In this application, it is desired to deliver a therapeutic agent to the site of arterial injury. The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent. The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks, and be as thin as possible so as to minimize the increase in profile. In addition, the coating material should not contribute to any adverse response by the body (i.e., should be non-thrombogenic, non-inflammatory, etc.). To date, the ideal coating material has not been developed for this application.

An alternative would be to design the stent to contain reservoirs which could be loaded with the drug. A coating or membrane of biocompatable material could be applied over the reservoirs which would control the diffusion of the drug from the reservoirs to the artery wall.

One advantage of this system is that the properties of the coating can be optimized for achieving superior biocompatibility and adhesion properties, without the addition requirement of being able to load and release the drug. The size, shape, position, and number of reservoirs can be used to control the amount of drug, and therefore the dose delivered.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be better understood in connection with the following figures in which FIGS. **1** and **1A** are top views and section views of a stent containing reservoirs as described in the present invention;

FIGS. **2***a* and **2***b* are similar views of an alternate embodiment of the stent with open ends;

FIGS. **3***a* and **3***b* are further alternate figures of a device containing a grooved reservoir; and

FIG. **4** is a layout view of a device containing a reservoir as in FIG. **3**.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents. Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty. The calcium antagonists have also been unsuccessful in preventing restenosis, although they are still under study. Other agents currently under study include thromboxane inhibitors, prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al., 42 Ann. Rev. Med., 127–132 (1991); Popma et al., 84 Circulation, 1426–1436 (1991)).

Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements, thromboxane receptor antagonists, cholesterol lowering agents, and serotonin antagonists has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Franklin, S. M. and Faxon, D. P., 4 Coronary Artery Disease, 2-32-242 (1993); Serruys, P. W. et al., 88 Circulation, (part 1) 1588–1601, (1993).

Conversely, stents have proven useful in preventing reducing the proliferation of restenosis. Stents, such as the stent **10** seen in layout in FIG. **4**, balloon-expandable slotted metal tubes (usually but not limited to stainless steel), which when expanded within the lumen of an angioplastied coronary artery, provide structural support to the arterial wall. This support is helpful in maintaining an open path for blood flow. In two randomized clinical trials, stents were shown to increase angiographic success after PTCA, increase the stenosed blood vessel lumen and to reduce the lesion recurrence at 6 months (Serruys et al., 331 New Eng Jour. Med, 495, (1994); Fischman et al., 331 New Eng Jour. Med, 496–501 (1994). Additionally, in a preliminary trial, heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Additionally, heparin coating appears to have the added benefit of producing a reduction

in sub-acute thrombosis after stent implantation (Serruys et al., 93 Circulation, 412–422, (1996). Thus, 1) sustained mechanical expansion of a stenosed coronary artery has been shown to provide some measure of restenosis prevention, and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs to local, injured tissue off the surface of the stent.

Numerous agents are being actively studied as antiproliferative agents for use in restenosis and have shown some activity in experimental animal models. These include: heparin and heparin fragments (Clowes and Karnovsky, 265 Nature, 25–626, (1977); Guyton, J. R. et al. 46 Circ. Res., 625–634, (1980); Clowes, A. W. and Clowes, M. M., 52 Lab. Invest., 611–616, (1985); Clowes, A. W. and Clowes, M. M., 58 Circ. Res., 839–845 (1986);. Majesky et al., 61 Circ Res., 296–300, (1987); Snow et al., 137 Am. J. Pathol., 313–330 (1990); Okada, T. et al., 25 Neurosurgery, 92–898, (1989) colchicine (Currier, J. W. et al., 80 Circulation, 11–66, (1989), taxol (ref), agiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., 245 Science, 186–188 (1989), angiopeptin (Lundergan, C. F. et al., 17 Am. J. Cardiol. (Suppi. B); 132B-136B (1991), Cyclosporin A (Jonasson, L. et. al., 85 Proc. Nati, Acad. Sci., 2303 (1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., 253 Science, 1129–1132 (1991), terbinafine (Nemecek, G. M. et al., 248 J. Pharmacol. Exp. Thera., 1167–11747 (1989), trapidil (Liu, M. W. et al., 81 Circulation, 1089–1093 (1990), interferon-gamma (Hansson, G. K. and Holm, 84 J. Circulation, 1266–1272 (1991), steroids (Colburn, M. D. et al., 15 J. Vasc. Surg., 510–518 (1992), see also Berk, B. C. et al., 17 J. Am. Coll. Cardiol., 111B-117B (1991), ionizing radiation (ref), fusion toxins (ref) antisense oligonucleotides (ref), gene vectors (ref), and rapamycin (see below).

Of particular interest in rapamycin. Rapamycin is a macrolide antibiotic which blocks IL-2-mediated T-cell proliferation and possesses antiinflammatory activity. While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G.sub.1 to 5 phase progression of T-cells through the cell cycle by inhibiting specific cell cyclins and cyclin-dependent protein kinases (Siekierka, Immunol. Res. 13: 110–116, 1994). The antiproliferative action of rapamycin is not limited to T-cells; Marx et al. (Circ Res 76:412–417, 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC in vitro while Poon et al. have shown the rat, porcine, and human SMC migratin can also be inhibited by rapamycin (J Clin Invest 98: 2277–2283, 1996). Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response. In fact, the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in a rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al., Transplantation 55:1409–1418, 1993; Gallo et al., in press, (1997)). These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis.

Although the ideal agent for restenosis has not yet been identified, some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury, including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications. Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of SMC combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

Experiments

Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression.

Delivery Methods: These can vary:

- Local delivery of such agents (rapamycin) from the struts of a stent, from a stent graft, grafts, stent cover or sheath.
- Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft.
- or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein.
- or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e.g. vapour deposition methods such as rf-plasma polymerization) and combinations thereof.
- Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake.
- Extravascular delivery by the pericardial route.
- Extravascular delivery by the advential application of sustained release formulations.

Uses:

- for inhibition of cell proliferation to prevent neointimal proliferation and restenosis.
- prevention of tumor expansion from stents.
- preventingrowth of tissue into catheters and shunts inducing their failure.

1. Experimental Stent Delivery Method—Delivery from Polymer Matrix:

Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0.001 weight % to 30 weight % of drug. Polymers are biocompatible (i.e., not elicit any negative tissue reaction or promote mural thrombus formation) and degradable, such as lactone-based polyesters or copolyesters, e.g., polylactide, polycaprolactonglycolide, polyorthoesters, polyanhydrides; poly-amino acids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, e.g., PEO-PLLA, or blends thereof. Nonabsorbable biocompatible polymers are also suitable candidates. Polymers such as polydimethylsiolxane; poly(ethylene-vingylacetate); acrylate based polymers or copolymers, e.g., poly(hydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters.

Polymer/drug mixture is applied to the surfaces of the stent by either dip-coating, or spray coating, or brush coating or dip/spin coating or combinations thereof, and the solvent allowed to evaporate to leave a film with entrapped rapamycin.

2. Experimental Stent Delivery Method—Delivery from Microporous Depots in Stent Through a Polymer Membrane Coating:

Stent, whose body has been modified to contain micropores or channels is dipped into a solution of Rapamycin, range 0.001 wt % to saturated, in organic solvent such as acetone or methylene chloride, for sufficient time to allow solution to permeate into the pores. (The dipping solution can also be compressed to improve the loading efficiency.) After solvent has been allowed to evaporate, the stent is dipped briefly in fresh solvent to remove excess surface bound drug. A solution of polymer, chosen from any identified in the first experimental method, is applied to the

stent as detailed above. This outer layer of polymer will act as diffusion-controller for release of drug.

3. Experimental Stent Delivery Method—Delivery Via Lysis of a Covalent Drug Tether:

Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization. Covalent bonds such as ester, amides or anhydrides may be suitable for this.

4. Experimental Method—Pericardial Delivery:

A: Polymeric Sheet

Rapamycin is combined at concentration range previously highlighted, with a degradable polymer such as poly(caprolactone-gylcolid-e) or non-degradable polymer, e.g., polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10.mu. to 1000.mu. The resulting sheet can be wrapped perivascularly on the target vessel. Preference would be for the absorbable polymer.

B: Conformal Coating:

Rapamycin is combined with a polymer that has a melting temperature just above 37° C., range 40°–45° C. Mixture is applied in a molten state to the external side of the target vessel. Upon cooling to body temperature the mixture solidifies conformably to the vessel wall. Both non-degradable and absorbable biocompatible polymers are suitable.

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin. As seen in FIGS. **1***a*, **2***a* and **3***a*, any stent strut **10**, **20**, **30** can be modified to have a certain reservoir or channel **11**, **21**, **31**. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. FIG. **4** shows a stent **40** with a reservoir **45** created at the apex of a flexible strut. Of course, this reservoir **45** is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents.

In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must be kept at a size of about 0.0005" to about 0.003". Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

These and other concepts will are disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be perceived to fall within the scope of the invention which is to be realized from the attached claims and their equivalents.

What is claimed:

1. A device comprising a metallic stent, a biocompatible, nonabsorbable polymeric carrier, and a therapeutic agent, wherein:

said polymeric carrier comprises an acrylate-based polymer or copolymer, a fluorinated polymer, or a mixture thereof, and

said therapeutic agent is rapamycin, or a macrocyclic lactone analog thereof, and is present in an amount effective to inhibit neointimal proliferation.

2. The device according to claim **1** wherein said therapeutic agent is a macrocyclic lactone analog of rapamycin.

3. The device according to claim **1** that provides a controlled release of said therapeutic agent over a period of several weeks.

4. The device according to claim **2** that provides a controlled release of said therapeutic agent over a period of several weeks.

5. A method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting a device according to any one of claims **1** to **4** in the lumen of said coronary artery.

* * * * *

Exhibit E

US007223286B2

(12) **United States Patent**
Wright et al.

(10) **Patent No.: US 7,223,286 B2**
(45) **Date of Patent: *May 29, 2007**

(54) **LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT**

(75) Inventors: **Carol Wright**, Somerset, NJ (US); **Gerard H. Llanos**, Stewartsville, NJ (US); **Ronald Rakos**, Neshanic Station, NJ (US); **Kristin King**, Mahwah, NJ (US); **Robert Falotico**, Bell Mead, NJ (US)

(73) Assignee: **Cordis Corporation**, Miami Lakes, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 265 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/951,385**

(22) Filed: **Sep. 28, 2004**

(65) **Prior Publication Data**

US 2005/0085902 A1 Apr. 21, 2005

Related U.S. Application Data

(63) Continuation of application No. 10/408,328, filed on Apr. 7, 2003, now Pat. No. 6,808,536, which is a continuation of application No. 09/874,117, filed on Jun. 4, 2001, now Pat. No. 6,585,764, which is a continuation of application No. 09/061,568, filed on Apr. 16, 1998, now Pat. No. 6,273,913.

(60) Provisional application No. 60/044,692, filed on Apr. 18, 1997.

(51) **Int. Cl.**
A61F 2/06 (2006.01)

(52) **U.S. Cl.** **623/1.42**

(58) **Field of Classification Search** 623/1.42–1.48; 427/2.1–2.31
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

861,659	A	7/1907	Johnston	464/147
3,051,677	A	8/1962	Rexford	522/156
3,279,996	A	10/1966	Long et al.	424/424
3,526,005	A	9/1970	Bokros	623/11.11
3,599,641	A	8/1971	Sheridan	604/256
3,657,744	A	4/1972	Ersek	128/898

(Continued)

FOREIGN PATENT DOCUMENTS

DE 3205942 A1 9/1983

(Continued)

OTHER PUBLICATIONS

U.S. Appl. No. 07/819,314, filed Jan. 9, 1992, Morris.

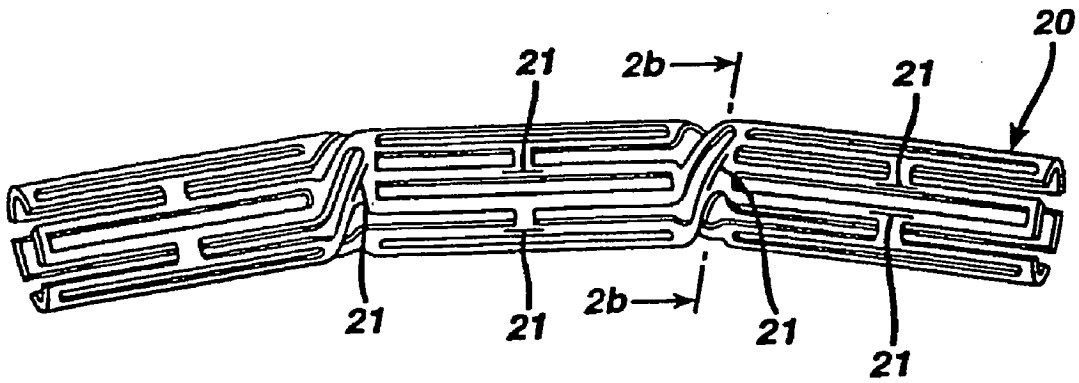
(Continued)

Primary Examiner—Suzette Gherbi
(74) *Attorney, Agent, or Firm*—Woodcock Washburn LLP

(57) **ABSTRACT**

Methods of preparing intravascular stents with a polymeric coating containing macrocyclic lactone (such as rapamycin or its analogs), stents and stent graphs with such coatings, and methods of treating a coronary artery with such devices. The macrocyclic lactone-based polymeric coating facilitates the performance of such devices in inhibiting restenosis.

77 Claims, 2 Drawing Sheets



U.S. PATENT DOCUMENTS

3,744,596	A	7/1973	Sander	188/203
3,779,805	A	12/1973	Alsberg	427/105
3,929,992	A	12/1975	Sehgal et al.	424/122
3,932,627	A	1/1976	Margraf	514/56
3,948,254	A	4/1976	Zaffaroni	128/833
3,952,334	A	4/1976	Bokros et al.	623/11.11
3,968,800	A	7/1976	Vilasi	606/198
4,069,307	A	1/1978	Higuchi et al.	424/432
4,076,285	A	2/1978	Martinez	285/332
4,292,965	A	10/1981	Nash et al.	128/833
4,299,226	A	11/1981	Banka	604/509
4,300,244	A	11/1981	Bokros	623/1.13
4,312,920	A	1/1982	Pierce et al.	428/425.5
4,321,711	A	3/1982	Mano	623/1.43
4,323,071	A	4/1982	Simpson et al.	606/194
4,390,599	A	6/1983	Broyles	428/597
4,413,359	A	11/1983	Akiyama et al.	623/23.72
4,423,183	A	12/1983	Close	524/546
4,441,216	A	4/1984	Ionescu et al.	623/2.19
4,503,569	A	3/1985	Dotter	623/1.19
4,512,338	A	4/1985	Balko et al.	606/108
4,550,447	A	11/1985	Seiler, Jr. et al.	623/1.32
4,553,545	A	11/1985	Maass et al.	606/198
4,560,374	A	12/1985	Hammerslag	604/509
4,562,596	A	1/1986	Kornberg	623/1.32
4,565,740	A	1/1986	Golander et al.	428/409
4,580,568	A	4/1986	Gianturco	606/198
4,613,665	A	9/1986	Larm	536/20
4,642,111	A	2/1987	Sakamoto et al.	424/492
4,655,771	A	4/1987	Wallsten	623/1.22
4,656,083	A	4/1987	Hoffman et al.	442/123
4,676,241	A	6/1987	Webb et al.	128/207.14
4,678,466	A	7/1987	Rosenwald	424/427
4,687,482	A	8/1987	Hanson	623/1.49
4,689,046	A	8/1987	Bokros	623/2.31
4,731,054	A	3/1988	Billeter et al.	604/93.01
4,733,665	A	3/1988	Palmaz	606/108
4,739,762	A	4/1988	Palmaz	623/1.11
4,740,207	A	4/1988	Kreamer	623/1.15
4,749,585	A	6/1988	Greco et al.	428/422
4,753,652	A	6/1988	Langer et al.	623/1.42
4,760,849	A	8/1988	Kropf	606/191
4,768,507	A	9/1988	Fischell et al.	623/1.11
4,776,337	A	10/1988	Palmaz	623/1.11
4,786,500	A	11/1988	Wong	424/422
4,787,899	A	11/1988	Lazarus	623/1.11
4,800,882	A	1/1989	Gianturco	606/194
4,810,784	A	3/1989	Larm	536/20
4,856,516	A	8/1989	Hillstead	606/194
4,871,357	A	10/1989	Hsu et al.	604/266
4,872,867	A	10/1989	Joh	604/269
4,876,109	A	10/1989	Mayer et al.	604/269
4,886,062	A	12/1989	Wiktor	606/194
4,907,336	A	3/1990	Gianturco	29/515
4,916,193	A	4/1990	Tang et al.	525/413
4,954,126	A	9/1990	Wallsten	600/36
4,969,458	A	11/1990	Wiktor	623/1.11
4,990,131	A	2/1991	Dardik et al.	600/36
4,990,155	A	2/1991	Wilkoff	606/191
4,994,071	A	2/1991	MacGregor	606/194
4,994,298	A	2/1991	Yasuda	427/490
4,998,923	A	3/1991	Samson et al.	606/194
5,015,253	A	5/1991	MacGregor	623/1.15
5,019,090	A	5/1991	Pinchuk	623/1.15
5,019,096	A	5/1991	Fox, Jr. et al.	600/36
5,029,877	A	7/1991	Fedeli	277/354
5,034,265	A	7/1991	Hoffman et al.	442/126
5,035,706	A	7/1991	Giantureo et al.	606/198
5,041,100	A	8/1991	Rowland et al.	604/265
5,041,126	A	8/1991	Gianturco	623/1.15
5,047,020	A	9/1991	Hsu	604/266
5,049,132	A	9/1991	Shaffer et al.	604/101.02
5,049,403	A	9/1991	Larm et al.	427/2.1
5,053,048	A	10/1991	Pinchuk	623/1.43
5,059,166	A	10/1991	Fischell et al.	600/3
5,061,275	A	10/1991	Wallsten et al.	623/1.22
5,061,750	A	10/1991	Feijen et al.	525/54.1
5,064,435	A	11/1991	Porter	623/23.7
5,092,877	A	3/1992	Pinchuk	128/898
5,102,417	A	4/1992	Palmaz	606/195
5,104,404	A	4/1992	Wolff	623/1.16
5,116,365	A	5/1992	Hillstead	623/1.15
5,122,154	A	6/1992	Rhodes	623/1.13
5,131,908	A	7/1992	Dardik et al.	600/36
5,133,732	A	7/1992	Wiktor	623/1.22
5,134,192	A	7/1992	Feijen et al.	525/54.1
5,135,536	A	8/1992	Hillstead	606/195
5,163,952	A	11/1992	Froix	623/1.18
5,163,958	A	11/1992	Pinchuk	623/23.49
5,171,217	A	12/1992	March et al.	604/507
5,171,262	A	12/1992	MacGregor	623/1.15
5,176,660	A	1/1993	Truckai	604/527
5,176,972	A	1/1993	Bloom et al.	430/14
5,178,618	A	1/1993	Kandarpa	606/28
5,180,366	A	1/1993	Woods	604/96.01
5,182,317	A	1/1993	Winters et al.	523/112
5,185,408	A	2/1993	Tang et al.	525/415
5,192,307	A	3/1993	Wall	623/1.2
5,195,984	A	3/1993	Schatz	623/1.2
5,213,576	A	5/1993	Abiuso et al.	604/103.01
5,213,898	A	5/1993	Larm et al.	428/422
5,217,483	A	6/1993	Tower	623/1.15
5,222,971	A	6/1993	Willard et al.	606/198
5,226,913	A	7/1993	Pinchuk	140/71 R
5,234,456	A	8/1993	Silvestrini	623/1.2
5,246,445	A	9/1993	Yachia et al.	623/1.2
5,258,020	A	11/1993	Froix	128/898
5,258,021	A	11/1993	Duran	623/2.3
5,262,451	A	11/1993	Winters et al.	523/112
5,266,073	A	11/1993	Wall	623/1.2
5,272,012	A	12/1993	Opolski	428/423.1
4,733,665	A	1/1994	Palmaz	606/108
5,275,622	A	1/1994	Lazarus et al.	623/1.11
5,282,823	A	2/1994	Schwartz et al.	623/1.22
5,282,824	A	2/1994	Gianturco	623/1.13
5,283,257	A	2/1994	Gregory et al.	514/458
5,288,711	A	2/1994	Mitchell et al.	424/122
5,290,305	A	3/1994	Inoue	623/1.2
5,292,331	A	3/1994	Boneau	623/1.16
5,292,802	A	3/1994	Rhee et al.	525/54.1
5,304,121	A	4/1994	Sahatjian	604/509
5,304,200	A	4/1994	Spaulding	623/1.16
5,306,250	A	4/1994	March et al.	604/104
5,308,862	A	5/1994	Ohlstein	514/411
5,308,889	A	5/1994	Rhee et al.	523/113
5,314,444	A	5/1994	Gianturco	606/195
5,314,472	A	5/1994	Fontaine	623/1.22
5,328,471	A	7/1994	Slepian	604/101.03
5,334,301	A	8/1994	Heinke et al.	204/267
5,336,518	A	8/1994	Narayanan et al.	427/470
5,338,770	A	8/1994	Winters et al.	523/112
5,342,348	A	8/1994	Kaplan	604/891.1
5,342,387	A	8/1994	Summers	606/198
5,342,621	A	8/1994	Eury	606/198
5,354,257	A	10/1994	Roubin et al.	600/7
5,354,308	A	10/1994	Simon et al.	623/1.15
5,356,433	A	10/1994	Rowland et al.	424/422
5,366,504	A	11/1994	Andersen et al.	623/1.5
5,368,566	A	11/1994	Crocker	604/101.02
5,370,683	A	12/1994	Fontaine	623/1.22
5,370,691	A	12/1994	Samson	623/1.22
5,375,612	A	12/1994	Cottenceau et al.	128/899
5,376,112	A	12/1994	Duran	623/1.26
5,378,475	A	1/1995	Smith et al.	424/473

5,380,299	A	1/1995	Fearnot et al.	604/265
5,382,261	A	1/1995	Palmaz	606/158
5,383,853	A	1/1995	Jung et al.	604/103.04
5,383,928	A	1/1995	Scott et al.	623/1.12
5,387,235	A	2/1995	Chuter	623/1.11
5,389,106	A	2/1995	Tower	623/1.15
5,393,772	A	2/1995	Yue et al.	514/410
5,395,390	A	3/1995	Simon et al.	623/1.18
5,397,355	A	3/1995	Marin et al.	623/1.2
5,399,352	A	3/1995	Hanson	424/423
5,403,341	A	4/1995	Solar	606/198
5,405,377	A	4/1995	Cragg	623/1.2
5,409,696	A	4/1995	Narayanan et al.	424/78.17
5,411,549	A	5/1995	Peters	623/1.15
5,415,619	A	5/1995	Lee et al.	600/36
5,417,969	A	5/1995	Hsu et al.	424/78.27
5,419,760	A	5/1995	Narciso, Jr.	604/8
D359,802	S	6/1995	Fontaine	D24/155
5,421,955	A	6/1995	Lau et al.	216/48
5,423,885	A	6/1995	Williams	623/1.17
5,429,618	A	7/1995	Keogh	604/266
5,429,634	A	7/1995	Narciso, Jr.	604/890.1
5,439,446	A	8/1995	Barry	604/103.01
5,441,515	A	8/1995	Khosravi et al.	606/194
5,441,516	A	8/1995	Wang et al.	606/198
5,441,947	A	8/1995	Dodge et al.	514/179
5,443,458	A	8/1995	Evry	604/891.1
5,443,477	A	8/1995	Marin et al.	606/198
5,443,496	A	8/1995	Schwartz et al.	623/1.16
5,443,498	A	8/1995	Fontaine	623/1.17
5,443,500	A	8/1995	Sigwart	623/1.17
5,447,724	A	9/1995	Helmus et al.	424/426
5,449,372	A	9/1995	Schmaltz et al.	606/198
5,449,373	A	9/1995	Pinchasik et al.	606/198
5,449,382	A	9/1995	Dayton	623/1.15
5,464,450	A	11/1995	Buscemi et al.	632/1.2
5,464,540	A	11/1995	Friesen et al.	210/640
5,464,650	A	11/1995	Berg et al.	427/2.3
5,474,563	A	12/1995	Myler et al.	606/108
5,486,357	A	1/1996	Narayanan	424/78.17
5,496,365	A	3/1996	Sgro	623/1.2
5,500,013	A	3/1996	Buscemi et al.	623/1.22
5,510,077	A	4/1996	Dinh et al.	264/485
5,512,055	A	4/1996	Domb et al.	604/265
5,516,781	A	5/1996	Morris et al.	514/291
5,519,042	A	5/1996	Morris et al.	514/378
5,523,092	A	6/1996	Hanson et al.	424/423
5,527,354	A	6/1996	Fontaine et al.	623/1.17
5,545,208	A	8/1996	Wolff et al.	623/1.22
5,551,954	A	9/1996	Buscemi et al.	623/1.15
5,554,182	A	9/1996	Dinh et al.	600/36
5,554,954	A	9/1996	Takahashi	327/546
5,556,413	A	9/1996	Lam	623/1.2
5,562,922	A	10/1996	Lambert	424/486
5,563,146	A	10/1996	Morris	514/291
5,569,197	A	10/1996	Helmus	604/102.02
5,569,295	A	10/1996	Lam	606/198
5,569,462	A	10/1996	Martinson et al.	424/423
5,569,463	A	10/1996	Helmus et al.	424/426
5,571,089	A	11/1996	Crocker	
5,571,166	A	11/1996	Dinh et al.	128/898
5,574,059	A	11/1996	Regunathan et al.	514/397
5,575,818	A	11/1996	Pinchuk	623/1.15
5,578,075	A	11/1996	Dayton	623/1.15
5,580,873	A	12/1996	Bianco et al.	514/263.36
5,580,874	A	12/1996	Bianco et al.	514/263.36
5,591,140	A	1/1997	Narayanan et al.	604/269
5,591,197	A	1/1997	Orth et al.	
5,591,224	A	1/1997	Schwartz et al.	623/1.22
5,591,227	A	1/1997	Dinh et al.	623/1.22
5,599,352	A	2/1997	Dinh et al.	128/898
5,603,722	A	2/1997	Phan et al.	623/1.18
5,604,283	A	2/1997	Wada et al.	524/236
5,605,696	A	2/1997	Eury et al.	424/423
5,607,463	A	3/1997	Schwartz et al.	623/1.44
5,607,475	A	3/1997	Cahalan et al.	424/423
5,609,629	A	3/1997	Fearnot et al.	623/1.42
5,616,608	A	4/1997	Kinsella et al.	514/449
5,620,984	A	4/1997	Bianco et al.	514/263.36
5,621,102	A	4/1997	Bianco et al.	544/267
5,622,975	A	4/1997	Singh et al.	514/324
5,624,411	A	4/1997	Tuch	604/265
5,628,785	A	5/1997	Schwartz et al.	128/898
5,629,077	A	5/1997	Turnlund et al.	623/1.15
5,629,315	A	5/1997	Bianco et al.	514/263.36
5,632,763	A	5/1997	Glastra	623/1.15
5,632,771	A	5/1997	Boatman et al.	623/1.15
5,632,776	A	5/1997	Kurumatani et al.	424/423
5,632,840	A	5/1997	Campbell	156/196
5,635,201	A	6/1997	Fabo	424/443
5,637,113	A	6/1997	Tartaglia et al.	623/1.42
5,643,312	A	7/1997	Fischell et al.	623/1.15
5,643,939	A	7/1997	Ohlstein	514/411
5,646,160	A	7/1997	Morris et al.	514/291
5,648,357	A	7/1997	Bianco et al.	514/263.36
5,649,952	A	7/1997	Lam	623/1.15
5,649,977	A	7/1997	Campbell	623/1.15
5,651,174	A	7/1997	Schwartz et al.	29/527.2
5,652,243	A	7/1997	Bianco et al.	514/263.36
5,653,747	A	8/1997	Dereume	623/1.54
5,653,992	A	8/1997	Bezwada et al.	424/426
5,662,609	A	9/1997	Slepian	604/101.03
5,665,591	A *	9/1997	Sonenshein et al.	435/375
5,665,728	A	9/1997	Morris et al.	424/122
5,667,764	A	9/1997	Kopia et al.	424/1.45
5,669,924	A	9/1997	Shaknovich	623/1.11
5,670,506	A	9/1997	Leigh et al.	514/141
5,672,638	A	9/1997	Verhoeven et al.	523/112
5,674,242	A	10/1997	Phan et al.	606/198
5,679,400	A	10/1997	Tuch	427/2.14
5,679,659	A	10/1997	Verhoeven et al.	514/56
5,684,061	A	11/1997	Ohnishi et al.	523/114
5,691,311	A	11/1997	Maraganore et al.	514/12
5,693,085	A	12/1997	Buirge et al.	623/1.13
5,697,967	A	12/1997	Dinh et al.	128/898
5,697,971	A	12/1997	Fischell et al.	623/1.15
5,700,286	A	12/1997	Tartaglia et al.	623/1.15
5,707,385	A	1/1998	Williams	606/192
5,709,874	A	1/1998	Hanson et al.	424/423
5,713,949	A	2/1998	Jayaraman	623/1.12
5,716,981	A	2/1998	Hunter et al.	514/449
5,725,549	A	3/1998	Lam	623/1.15
5,725,567	A	3/1998	Wolff et al.	623/1.42
5,728,150	A	3/1998	McDonald et al.	623/1.15
5,728,420	A	3/1998	Keogh	427/2.12
5,731,326	A	3/1998	Hart et al.	514/323
5,733,327	A	3/1998	Igaki et al.	623/1.5
5,733,920	A	3/1998	Mansuri et al.	514/337
5,733,925	A	3/1998	Kunz et al.	514/449
5,735,897	A	4/1998	Buirge	623/1.15
5,739,138	A	4/1998	Bianco et al.	514/263.36
5,755,734	A	5/1998	Richter et al.	606/194
5,755,772	A	5/1998	Evans et al.	128/898
5,759,205	A	6/1998	Valentini	433/173
5,769,883	A	6/1998	Buscemi et al.	623/1.42
5,776,184	A	7/1998	Tuch	623/1.11
5,780,476	A	7/1998	Underiner et al.	514/263.36
5,782,908	A	7/1998	Cahalan et al.	623/1.13
5,788,979	A	8/1998	Alt et al.	424/426
5,792,106	A	8/1998	Mische	604/103.01
5,792,772	A	8/1998	Bianco et al.	514/263.36
5,798,372	A	8/1998	Davies et al.	514/356
5,799,384	A	9/1998	Schwartz et al.	29/458
5,800,507	A	9/1998	Schwartz	623/1.11
5,800,508	A	9/1998	Goicoechea et al.	623/1.15
5,807,861	A	9/1998	Klein et al.	514/263.35

5,811,447	A	9/1998	Kunz et al.	514/411
5,820,917	A	10/1998	Tuch	427/2.1
5,820,918	A	10/1998	Ronan et al.	427/2.1
5,824,048	A	10/1998	Tuch	128/898
5,824,049	A	10/1998	Ragheb et al.	623/1.44
5,827,587	A	10/1998	Fukushi	428/36.6
5,833,651	A	11/1998	Donovan et al.	604/509
5,837,008	A	11/1998	Berg et al.	427/2.21
5,837,313	A	11/1998	Ding et al.	427/2.21
5,843,120	A	12/1998	Israel et al.	
5,843,166	A	12/1998	Lentz et al.	
5,843,172	A	12/1998	Yan	623/1.42
5,849,034	A	12/1998	Schwartz	606/36
5,851,217	A	12/1998	Wolff et al.	606/191
5,851,231	A	12/1998	Wolff et al.	623/1.42
5,858,990	A	1/1999	Walsh	514/44
5,861,027	A	1/1999	Trapp	623/1.15
5,865,814	A	2/1999	Tuch	623/1.15
5,871,535	A	2/1999	Wolff et al.	128/898
5,873,904	A	2/1999	Ragheb et al.	623/1.13
5,876,433	A	3/1999	Lunn	623/1.15
5,877,224	A	3/1999	Brocchini et al.	514/772.2
5,879,697	A	3/1999	Ding et al.	424/422
5,882,335	A	3/1999	Leone et al.	604/103.02
5,891,108	A	4/1999	Leone et al.	
5,893,840	A	4/1999	Hull et al.	604/103.02
5,897,911	A	4/1999	Loeffler	427/2.25
5,900,246	A	5/1999	Lambert	424/429
5,902,266	A	5/1999	Leone et al.	604/509
5,916,910	A	6/1999	Lai	514/423
5,922,393	A	7/1999	Jayaraman	427/2.3
5,932,243	A	8/1999	Fricker et al.	
5,932,299	A	8/1999	Katoot	427/508
5,932,580	A	8/1999	Levitzki et al.	181/152
5,951,586	A	9/1999	Berg et al.	606/198
5,957,971	A	9/1999	Schwartz	623/1.15
5,968,091	A	10/1999	Pinchuk et al.	623/1.16
5,972,027	A	10/1999	Johnson	
5,976,534	A	11/1999	Hart et al.	424/145.1
5,977,163	A	11/1999	Li et al.	514/449
5,980,553	A	11/1999	Gray et al.	623/1.15
5,980,566	A	11/1999	Alt et al.	623/23.7
5,980,972	A	11/1999	Ding	427/2.24
5,981,568	A	11/1999	Kunz et al.	514/411
5,985,307	A	11/1999	Hanson et al.	424/423
5,997,468	A	12/1999	Wolff et al.	606/36
6,004,346	A	12/1999	Wolff et al.	623/23.71
6,015,432	A	1/2000	Rakos et al.	623/1.13
6,039,721	A	3/2000	Johnson et al.	604/508
6,059,813	A	5/2000	Vrba et al.	606/198
6,071,305	A	6/2000	Brown et al.	623/1.43
6,074,659	A	6/2000	Kunz et al.	424/423
6,080,190	A	6/2000	Schwartz	623/1.22
6,096,070	A	8/2000	Ragheb et al.	623/1.39
6,120,536	A	9/2000	Ding et al.	623/1.43
6,120,847	A	9/2000	Yang et al.	
6,136,798	A	10/2000	Cody et al.	514/141
6,140,127	A	10/2000	Sprague	435/395
6,146,358	A	11/2000	Rowe	604/103
6,153,252	A	11/2000	Hossainy et al.	427/2.3
6,159,488	A	12/2000	Nagler et al.	424/423
6,171,232	B1	1/2001	Papandreou et al.	600/36
6,171,609	B1	1/2001	Kunz	424/422
6,177,272	B1	1/2001	Nabel et al.	435/320.1
6,179,817	B1	1/2001	Zhong	604/265
6,193,746	B1	2/2001	Strecker	623/1.13
6,214,901	B1	4/2001	Chudzik et al.	523/113
6,225,346	B1	5/2001	Tang et al.	514/523
6,240,616	B1	6/2001	Yan	29/527.2
6,245,537	B1	6/2001	Williams et al.	435/135
6,251,920	B1	6/2001	Grainger et al.	514/319
6,254,632	B1	7/2001	Wu et al.	623/1.15
6,254,634	B1	7/2001	Anderson et al.	623/1.42
6,258,121	B1	7/2001	Yang et al.	623/1.46
6,268,390	B1	7/2001	Kunz	514/411
6,273,913	B1	8/2001	Wright et al.	623/1.42
6,284,305	B1	9/2001	Ding et al.	427/2.28
6,287,320	B1	9/2001	Slepian	606/194
6,287,628	B1	9/2001	Hossainy et al.	427/2.3
6,299,604	B1	10/2001	Ragheb et al.	604/265
6,306,144	B1	10/2001	Sydney et al.	606/108
6,306,166	B1	10/2001	Barry et al.	623/1.46
6,306,176	B1	10/2001	Whitbourne	623/23.59
6,306,421	B1	10/2001	Kunz et al.	424/423
6,309,380	B1	10/2001	Larson et al.	604/502
6,309,660	B1	10/2001	Hsu et al.	424/425
6,313,264	B1	11/2001	Caggiano et al.	530/350
6,316,018	B1	11/2001	Ding et al.	424/423
6,335,029	B1	1/2002	Kamath et al.	424/423
6,358,556	B1	3/2002	Ding et al.	427/2.24
6,369,039	B1	4/2002	Palasis et al.	424/93.2
6,379,382	B1	4/2002	Yang	623/1.42
6,387,121	B1	5/2002	Alt	623/1.15
6,403,635	B1	6/2002	Kinsella et al.	514/449
6,407,067	B1	6/2002	Schafer	514/19
6,517,858	B1	2/2003	Haberbosch et al.	424/424
6,517,889	B1	2/2003	Jayaraman	427/2.24
6,545,097	B2	4/2003	Pinchuk et al.	525/240
6,585,764	B2	7/2003	Wright et al.	623/1.42
6,620,194	B2	9/2003	Ding et al.	623/1.43
6,746,773	B2	6/2004	Llanos et al.	428/421
6,776,796	B2	8/2004	Llanos et al.	623/1.46
6,808,536	B2	10/2004	Wright et al.	623/1.42
2001/0007083	A1	7/2001	Roorda	623/1.15
2001/0029351	A1	10/2001	Falotico et al.	604/103.02
2001/0029660	A1	10/2001	Johnson	29/557
2001/0032014	A1	10/2001	Yang et al.	623/1.15
2001/0034363	A1	10/2001	Li et al.	514/449
2001/0037145	A1	11/2001	Guruwaiya et al.	623/1.15
2002/0010418	A1	1/2002	Lary et al.	604/101.04
2002/0032477	A1	3/2002	Helmus et al.	623/1.2
2002/0041899	A1	4/2002	Chudzik et al.	424/487
2002/0061326	A1	5/2002	Li et al.	424/424
2002/0068969	A1	6/2002	Shanley et al.	623/1.16
2002/0071902	A1	6/2002	Ding et al.	427/2.24
2002/0082680	A1	6/2002	Shanley et al.	623/1.16
2002/0082685	A1	6/2002	Sirhan et al.	623/1.42
2002/0091433	A1	7/2002	Ding et al.	623/1.2
2002/0095114	A1	7/2002	Palasis	604/96.01
2002/0099438	A1	7/2002	Furst	623/1.16
2002/0103526	A1	8/2002	Steinke	623/1.11
2002/0119178	A1	8/2002	Levesque et al.	424/423
2002/0123505	A1	9/2002	Molliston et al.	514/291
2002/0127327	A1	9/2002	Schwartz et al.	427/2.15
2002/0133222	A1	9/2002	Das	623/1.16
2002/0133224	A1	9/2002	Bajgar et al.	623/1.39
2002/0165608	A1	11/2002	Llanos	604/500
2002/0193475	A1	12/2002	Hossainy et al.	524/113
2003/0065377	A1	4/2003	Davila et al.	604/265
2003/0216699	A1	11/2003	Falotico	604/265
2004/0049265	A1	3/2004	Ding et al.	623/1.42
2004/0243097	A1	12/2004	Falotico et al.	604/500
2004/0260268	A1	12/2004	Falotico et al.	604/500
2005/0002986	A1	1/2005	Falotico et al.	424/426
2005/0004663	A1	1/2005	Llanos et al.	623/1.46
2005/0033261	A1	2/2005	Falotico et al.	604/500
2005/0106210	A1	5/2005	Ding et al.	424/423
2005/0187611	A1	8/2005	Ding et al.	623/1.15
2005/0208200	A1	9/2005	Ding et al.	427/2.25
2006/0088654	A1	4/2006	Ding et al.	427/2.21
2006/0089705	A1	4/2006	Ding et al.	623/1.15

FOREIGN PATENT DOCUMENTS

DE	19723723	A1	12/1998
EP	0 145 166	A2	6/1985

EP	0 177 330 A2	4/1986
EP	0 183 372 A1	6/1986
EP	0 221 570 A2	5/1987
EP	0 421 729 A2	4/1991
EP	0 540 290 A2	5/1993
EP	0 568 310 A1	11/1993
EP	0 604 022 A1	6/1994
EP	0 621 015 A1	10/1994
EP	0 623 354 A1	11/1994
EP	0 734 698 A2	3/1996
EP	0 712 615 A1	5/1996
EP	0 716 836 A1	6/1996
EP	0 734 721 A2	10/1996
EP	0 747 069 A2	12/1996
EP	0 761 251 A1	3/1997
EP	0 800 801 A1	10/1997
EP	0 540 290 B1	1/1998
EP	0 830 853 A1	3/1998
EP	0 815 803 A1	7/1998
EP	0 850 651 A2	7/1998
EP	0 938 878 A2	9/1999
EP	0 938 878 A3	9/1999
EP	0 950 386 A2	10/1999
EP	0 968 688 A1	1/2000
EP	0 633 032 B1	2/2001
EP	1 192 957 A2	4/2002
EP	1 588 726 A1	10/2005
EP	1 588 727 A1	10/2005
FR	566 807 A1	4/1992
GB	0 662 307 A2	12/1951
GB	1 205 743 A	9/1970
GB	2 135 585 A	9/1984
SU	660689	5/1979
SU	1457921	2/1989
WO	89/03232 A1	4/1989
WO	91/12779 A1	9/1991
WO	92/15286 A1	9/1992
WO	94/01056 A1	1/1994
WO	94/21308 A1	9/1994
WO	94/21309 A1	9/1994
WO	94/24961 A1	11/1994
WO	96/00272 A1	1/1996
WO	96/26689 A1	9/1996
WO	96/32907 A1	10/1996
WO	96/34580 A1	11/1996
WO	97/25000 A1	7/1997
WO	97/33534 A1	9/1997
WO	98/08463 A1	3/1998
WO	98/13344 A1	4/1998
WO	98/19628 A1	5/1998
WO	98/23228 A1	6/1998
WO	98/23244 A1	6/1998
WO	98/34669 A1	8/1998
WO	98/36784 A1	8/1998
WO	98/47447 A1	10/1998
WO	98/56312 A1	12/1998
WO	00/21584 A1	4/2000
WO	00/27445 A1	5/2000
WO	00/27455 A1	5/2000
WO	00/32255 A1	6/2000
WO	00/38754 A1	7/2000
WO	01/87342 A2	11/2001
WO	01/87372 A1	11/2001
WO	01/87373 A1	11/2001
WO	01/87376 A1	11/2001
WO	02/26139 A1	4/2002
WO	02/26271 A1	4/2002
WO	02/26280 A1	4/2002
WO	02/26281 A1	4/2002
WO	03/015664 A1	2/2003
WO	03/057218 A1	7/2003

OTHER PUBLICATIONS

U.S. Appl. No. 08/424,884, filed Apr. 19, 1995, Helmus et al.
U.S. Appl. No. 08/526,273, filed Sep. 11, 1995, Ding.
U.S. Appl. No. 08/730,542, filed Oct. 11, 1996, Helmus.
U.S. Appl. No. 09/575,480, filed May 19, 2000, Kopia.
U.S. Appl. No. 10/431,059, filed May 7, 2003, Falotico
Abraham, R. T., "Mammalian target of rapamycin: Immunosupressive drugs offer new insight into cell growth regulation," *Progress in Inflammation Research*, 2000, Switzerland.
Alvarado, R. et al., "Evaluation of Polymer-coated Balloon-expandable Stents in Bile Ducts," *Radiology*, 1989, 170, 975-978.
Bailey et al., "Polymer Coating of Palmaz-Schatz Stent Attenuates Vascular Spasm after Stent Placement," *Circulation*, 82:III-541 (1990).
Berk, B. C. et al., "Pharmacologic Roles of Heparin and Glucocorticoids to Prevent Restenosis After Coronary Angioplasty," *JACC*, May 1991, 17(6), 111B-117B.
Bertram, P. G. et al., "The 14-3-3 proteins positively regulate repamycin-sensitive signaling," *Current Biology*, 1998, 8, 1259-1267.
Biomaterials Science (B.D. Ratner, Ed.), Academic Press, New York, NY, pp. 228-238, 1996.
Campbell, G. R. et al., "Phenotypic Modulation of Smooth Muscle Cells in Primary Culture, Vascular Smooth Muscle Cells in Culture," *CRC Press*, 1987, 39-55.
Chang, M. W. et al., "Adenovirus-mediated Over-expression of the Cyclin/Cyclin-dependent Kinase inhibitor, p21 inhibits Vascular Smooth Muscle Cell Proliferation and Neointima Formation in the Rat Carotid Artery Model of Balloon Angioplasty," *J. Clin. Invest.*, 1995, 96, 2260-2268.
Chung, J. et al., "Rapamycin-FKBP specifically blocks growth-dependent activation of and signaling by the 70 kd S6 protein kinases," *Cell*, Jun. 26, 1992, 69(7), 1227-1236.
Clowes, A. W. et al., "Kinetics of cellular proliferation after arterial injury. IV. Heparin inhibits rat smooth muscle mitogenesis and migration," *Circ. Res.*, 1986, 58(6), 839-845.
Clowes, A. W. et al., Kinetics of Cellular Proliferation after Arterial Injury, *Laboratory Investigation*, 1985, 52(6), 611-616.
Clowes, A. W. et al., "Significance of quiescent smooth muscle migration in the injured rat carotid artery," *Circ Res*. 1985, 56(1), 139-145.
Clowes, A. W., "Suppression by heparin of smooth muscle cell proliferation in injured arteries," *Nature*, 1977, 265(5595), 625-626.
Colburn, M. D. et al., "Dose responsive suppression of myointimal hyperplasia by dexamethasone," *J. Vasc. Surg.*, 1992, 15, 510-518.
Curier, J. W. et al., "Colchicine Inhibits Restenosis After Iliac Angioplasty in the Artherosclerotic Rabbit," *Circ.*, 1989, 80(4), 11-66 (Abstract No. 0263).
Encyclopedia of Polymer Science and Engineering, vol. 7, Fluorocarbon Elastomers, p. 257-267, Mar. 1989.
Farb, A. et al., "Vascular smooth muscle cell cytotoxicity and sustained inhibition of neointimal formation by fibroblast growth factor 2-saporin fusion protein," *Circ. Res.*, 1997, 80, 542-550.
Ferns, G. A. A. et al., "Inhibition of Neointimal Smooth Muscle Accumulation After Angioplasty by an Antibody to PDGF," *Science*, 1991, 253, 1129-1132.
Fischman, D. L. et al., "A Randomized Comparison of Coronary-Stent Placement and Balloon Angioplasty in the Treatment of Coronary Artery Disease," *N. Eng. J. Med.*, Aug. 25, 1994, 331(8), 496-501.
Franklin, S. M. et al., "Pharmacologic prevention of restenosis after coronary angioplasty: review of the randomized clinical trials," *Coronary Artery Disease* Mar. 1993, 4(3), 232-242.
Fukuyama, J. et al., "Tranilast suppresses the vascular intimal hyperplasia after balloon injury in rabbits fed on a high-cholesterol diet," *Eur. J. Pharmacol.*, 1996, 318, 327-332.
Gregory, C. R. et al., "Repamycin Inhibits Arterial Intimal Thickening Caused by Both Alloimmune and Mechanical Injury," *Transplantation*, Jun. 1993, 55(6), 1409-1418.

Gregory, C. R. et al, "Treatment with Repamycin and Mycophenolic Acid Reduces Arterial Intimal Thickening Produced by Mechanical Injury and Allows Endothelial Replacement," *Transplantation*, Mar. 15, 1995, 59(5), 655-661.

Guyton, J. R. et al., "Inhibition of rat arterial smooth muscle cell proliferation by heparin. In vivo studies with anticoagulant and nonanticoagulant heparin," *Circ. Res.*, 1980, 46, 625-634.

Hansson, G. K. et al., "Interferon-γ Inhibits Arterial Stenosis After Injury," *Circ.*, 1991, 84, 1266-1272.

Hashemolhosseini, S. et al., "Rapamycin Inhibition of the G1 to S Transition Is Mediated by Effects on Cyclin D1 mRNA and Protein Stability," *J Biol Chem*, Jun. 5, 1998, 273, 14424-14429.

Jonasson, J. et al., "Cyclosporin A inhibits smooth muscle proliferation in the vascular response to injury," *Proc. Natl., Acad. Sci.*, 1988, 85, 2303-2306.

Lange, R. A. MD et al., "Restenosis After Coronary Balloon Angioplasty," *Annu. Rev. Med.*, 1991, 42, 127-132.

Liu, M. W. et al., "Trapidil in Preventing Restenosis After Balloon Angioplasty in the Atherosclerotic Rabbit," *Circ.*, 1990, 81, 1089-1093.

Liu, M. W., MD et al., "Restenosis After Coronary Angioplasty Potential Biologic Determinants and Role of Intimal Hyperplasia," *Circulation*, 1989, 79, 1374-1387.

Lundergan, C. F. et al., "Peptide inhibition of Myointimal Proliferation by Angiopeptin, a Somatostatin Analogue," *JACC*, May 1991, 17(6), 132B-136B.

Majesky, M. W. et al., "Heparin regulates smooth muscle S phase entry in the injured rat carotid artery," *Circ. Res.*, 1987, 61, 296-300.

Marx, S. O. et al., "Rapamycin-FKBP Inhibits Cell Cycle Regulators of Proliferation in Vascular Smooth Muscle Cells," *Circ. Res.*, 1995, 76, 412-417.

Nemecek, G. M. et al., "Terbinafine Inhibits the Mitogenic Response to Platelet-Derived Growth Factor in Vitro and Neoinimal Proliferation in Vivo," *J. Pharmacol. Exp. Thera.*, 1989, 248, 1167-1174.

Okada, T. et al., "Localized Release of Perivascular Heparin Inhibits Intimal Proliferation after Endothelial Injury without Systemic Anticoagulation," *Neurosurgery*, 1989, 25, 892-898.

Poon, M. et al., "Rapamycin Inhibits Vascular Smooth Muscle Cell Migration," *J. Clin Invest.*, Nov. 1996, 98(10), 2277-2283.

Popma, J. J. et al., "Clinical trials of restenosis after coronary angioplasty," *Circulation*, Sep. 1991, 84(3), 1426-1436.

Powell, J. S. et al., "Inhibitors of Angiotensin-Converting Enzyme Prevent Myoiintimal Proliferation After Vascular Injury," *Science*, 1989, 245, 186-188.

Rensing, B. J. et al., Coronary restenosis elimination with a sirolimus eluting stent, *European Heart Journal*, 2001, 22, 2125-2130.

Rodeck, C. et al., "Methods for the Transcervical Collection of Fetal Cells During the First Trimester of Pregnancy," *Prenatal Diagnosis*, 1995, 15, 933-942.

Ruef, J. MD, et al., "Flavopiridol Inhibits Muscle Cell Proliferation In Vitro and Neointimal Formation In Vivo After Carotid Injury in the Rat," From the Division of Cardiology and Sealy for Molecular Cardiology, University of Texas Medical Branch, Galveston; Accepted Apr. 9, 1999; *Circulation* Aug. 10, 1999, pp. 659-665.

Serruys, P. W. et al., "A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease," *N Engl J Med*, Aug. 25, 1994; 331(8), 489-495.

Serruys, P. W. et al., "Evaluation of ketanserin in the prevention of restenosis after percutaneous transluminal coronary angioplasty. A multicenter randomized double-blind placebo-controlled trial," *Circulation*. Oct. 1993; 88(4 Pt 1), 1588-1601.

Serruys, P. W. et al., "Heparin-coated Palmaz-Schatz stents in human coronary arteries. Early outcome of the Benestent-II Pilot Study," *Circulation*, Feb. 1, 1996; 93(3), 412-422.

Siekierka, J. J., "Probing T-Cell Signal Transduction Pathways with the Immunosupressive Drugs, FK-506 and Rapamycin," *Immunologic Research*, 1994, 13, 110-116.

Sigwart, et al., "Intravascular Stents to Prevent Occlusion and Restenosis After Transluminal Angioplasty," *N. Engl. J. Med.*, Mar. 19, 1987, 316, 701-706.

Simons, M. et al., "Antisense *c-myb* oligonucleotides inhibit intimal arterial smooth muscle cell accumulation in vivo," *Nature*, 1992, 359, 67-70.

Snow, A. D. et al., "Heparin modulates the composition of the extracellular matrix domain surrounding arterial smooth muscle cells," *Am. J. Pathol.*, 1990, 137, 313-330.

Sollott, S. J. et al., "Taxol Inhibits Neointimal Smooth Muscle Cell Accumulation after Angioplasty in the Rat," *J. Clin. Invest.*, 1995, 95, 1869-1876.

van Der Giessen, et al., "Self-expandable Mesh Stents: an Experimental Study Comparing Polymer Coated and Uncoated Wallstent Stents in the Coronary Circulation of Pigs," *Circulation* 1990, 82(suppl. III):III-542.

van Der Giessen, W. J. et al., "Coronary stenting with polymer-coated and uncoated self-expanding endoprosthesis in pigs," Coron. Art. Disease 1992; 3, 631-640.

Vasey, C. G. et al., "Clinical Cardiology: Stress Echo and Coronary Flow", , *Circulation*, Oct. 1989, 80(4) Supplement II, II-66.

Verweire, E. et al., "Evaluation of Fluorinated Polymers As Coronary Stent Coating," *Journal of Materials Science: Materials in Medicine*, Apr. 2000.

Weinberger, J. et al., "Intracoronary irradiation: dose response for the prevention of restenosis in swine," *Int. J. Rad. Onc. Biol. Phys.*, 1996, 36, 767-775.

Preliminary Amendment in U.S. Appl. No. 07/258,189, May 22, 1989.

Trial Transcript from Nov. 6, 2000 at 185-90 and 235-36 (Attorneys' opening remarks regarding '984 patent).

Trial Transcript from Nov. 7, 2000 at 274-301, 307-315, 320-28 and 332 (Cordis expert testimony regarding the Palmaz-Schatz stent); 370-379, 480-496 (J. Palmaz testimony regarding the Palmaz-Schatz stent, the '984 patent and the connected z-stent art).

Trial Transcript from Nov. 8, 2000 at 547-63, 657-63, 674-722, 782-85 (Cordis expert testimony regarding the Palmaz-Schatz stent, the '984 patent and the connected z-stent art).

Trial Transcript from Nov. 9, 2000 at 819-23, 921 (Cordis expert testimony regarding the '984 patent); 926-941. (R. Croce testimony re Palmaz-Schatz stent); 1033-1053. (R. Schatz testimony).

Trial Transcript from Nov. 13, 2000 at 1086-1 134. (R. Schatz testimony); 1275-1305 (Cordis expert testimony regarding the '984 patent).

Trial Transcript from Nov. 14, 2000 at 1390-1404, 1448-1454, 1486-1500 (Cordis expert testimony regarding the '984 patent).

Trial Transcript from Nov. 15, 2000 at 1686-87, 1724-42, 1828-34, 1850-54, 1887-92 (AVE expert testimony regarding the '984 patent).

Trial Transcript from Nov. 16, 2000 at 2077-198 (AVE expert testimony regarding the alleged obviousness of the '984 patent).

Trial Transcript from Nov. 17, 2000 at 2331-34 (jury instructions as to the meaning of the limitations of the claims of the '984 patent).

Trial Transcript from Nov. 20, 2000 at 2441-48, 2499-2500, 2546-50, 2552-56 (Attorneys' closing arguments regarding the '984 patent).

Trial Transcript from Nov. 21, 2000 at 2592-94 (reading of jury verdict).

Trial Transcript from Dec. 18, 2000 at 2750-95 (Cordis expert testimony regarding the Palmaz-Schatz stent during the damages phase).

Trial Transcript from Dec. 20, 2000 at 3421-88 (AVE expert testimony regarding the Palmaz-Schatz stent during the damages phase).

Jury verdict, dated Nov. 21, 2000.

District Court decisions on post-trial motions (194 F. Supp. 2d 323).

Court of Appeal for the Federal Circuit decision (339 F.3d 1352).

Trial Transcript from Mar. 4, 2005 at 133-135, 171-173 and 192-96 (Attorney's opening remarks regarding '984 validity).

Trial Transcript from Mar. 7, 2005 at 275-31 1 (Cordis expert testimony regarding the Palmaz-Schatz stent); 342-46, 353-59, 416-425 (J. Palmaz testimony regarding the Palmaz-Schatz stent, the '984 patent and the connected z-stent art); 430-449, 452-58, 462-492 (R. Croce testimony regarding the Palmaz-Schatz stent); 500-507 (Cordis expert testimony regarding the '984 patent).

Trial Transcript from Mar. 8, 2005 at 609 (Cordis expert testimony regarding the '984 patent); 628-73, 724-740, 773, 801-839 (Cordis expert testimony regarding the '984 patent), the prior art and the Palmaz-Schatz stent).
Trial Transcript from Mar. 9, 2005 at 936-49, 968-69 (Cordis expert testimony regarding the '984 patent, the prior art and the Palmaz-Schatz stent).
Trial Transcript from Mar. 10, 2005 at 1427-74, 178-1509, 1514-23 (AVE expert testimony regarding the alleged obviousness of the '984 patent); 1566-93 (AVE expert testimony regarding Palmaz-Schatz stent); 1634-49 (R. Schatz testimony).
Trial Transcript from Mar. 11, 2005 at 1846-47, 1891-1900, 1919 (Attorneys' closing arguments regarding '984 obviousness).
Trial Transcript from Mar. 14, 2005 at 1964-67 (reading of jury verdict).
Jury verdict dated Mar. 14, 2005.
Medtronic Vascular Inc.'s Opening Brief in Support of Its Motion for Judgement As A Infringement Claim dated Apr. 19, 2005.
Medtronic Vascular Inc.'s Opening Brief in Support of Its Motion for a New Trial dated Apr. 9, 2005.
D.I. 1407, Cordis' Combined Answering Brief In Opposition to AVE's Motion for JMOL on Infringement of the Palmaz '762 and Schatz '984 Patents and Its Motion for a New Trial dated May 5, 2005.
D.I. 1414, Medtronic Vascular Inc.'s Combined Reply Brief In Support of Its Motion for Judgement as a Matter of Law on Cordis Corp.'s Patent Infringement Claims and Its Motion for a New Trial dated May 19, 2005.
Trial Transcript from Feb. 8, 2001 at 372-412, 449-469 (B. Tobor testimony regarding the prosecution of the '417, '984 and '332 patents); 510-13 (J. Milnamow testimony regarding the prosecution of the '332 patent); 558-604 (J. Palmaz testimony regarding the prosecution of the '417, '984 and '332 patents and the prior art).
Trial Transcript from Feb. 9, 2001 at 637-45, 662-672, 682-85 (J. Palmaz testimony regarding the prior art); 699-742 (R. Schatz testimony); 769-770, 790-95 (Cordis expert testimony regarding prior art).
D.I. 1067, Medtronic AVE, Inc.'s Post-Trial Brief Relating to the Unenforceability of the '762 and '984 Patents Due to Inequitable Conduct.
D.I. 1077, Cordis' Combined Answering Brief in Opposition to AVE's BSC's Post-Hearing Briefs on Alleged Inequitable Conduct Concerning the '762, '984 and '332 Patents.
D.I. 1089, Reply Brief In Support of Medtronic AVE, Inc.'s Contention that the '762 and '984 Patents are Unenforceable Due to Inequitable Conduct dated May 7, 2001.
C.A. No. 00-886-SLR, Answer and Counterclaims of Def. Medtronic AVE, Inc. To First Amended Complaint of Plaintiff Cordis Corp.
BSC's Opening Post-Trial Brief in Support of Its Defense That the Patents in Suit Are Unenforceable, dated Mar. 16, 2001.
Reply Brief in Support of BSC's Defense That the Patents in Suit Are Unenforceable, dated May 7, 2001.
Court's Decision on allegations of inequitable conduct (194 F. Supp. 2d 323) Mar. 28, 2002.
Trial Transcript from Nov. 21, 2000 at 155-57 and 180-84 (Attorneys' opening remarks regarding '332 patent).
Trial Transcript from Nov. 27, 2000 at 227-51, 260-300 (Cordis expert testimony regarding the Palmaz-Schatz stent); 343-60, 363-67, 424-33 (J. Palmaz testimony regarding the Palmaz-Schatz stent and the '332 patent).
Trial Transcript from Nov. 28, 2000 at 649-71.
Trial Transcript from Nov. 29, 2000 at 791-816, 859-870, 953-62 (Cordis expert testimony regarding the '332 patent and the Palmaz-Schatz stent).
Trial Transcript from Nov. 30, 2000 at 1018 (Cordis expert testimony regarding the '332 patent); 1062-80, 1 108-1 1 1 1 (R. Croce testimony regarding the Palmaz-Schatz stent); 1 169-70, 1205-17, 1236-45 (Cordis expert testimony regarding the '332 patent).
Trial Transcript from Dec. 1, 2000 at 1352-54 (Cordis expert testimony regarding the '332 patent); 1364-1442 (R. Schatz testimony); 1493-1508, 1552-69 (BSC expert testimony regarding the '332 patent and the Palmaz-Schatz stent).
Trial Transcript from Dec. 4, 2000 at 1602-12, 1638-51, 1713-14, 1730-61, 1811-14, 1823-36 (BSC expert testimony regarding the alleged obviousness of the '332 patent, the prior art and the Palmaz-Schatz stent).
Trial Transcript from Dec. 6, 2000 at 2318-27, 2342-58 (BSC expert testimony regarding the '332 patent).
Trial Transcript from Dec. 7, 2000 at 2549-52 (Cordis expert testimony regarding the '332 patent); 2575-2579, 2591-92, 2630-31, 2649, 2669-71, 2684-85, 2688, 2708-10, 2725-27 (Attorney closing argument regarding '332 patent); 2742-46 Q'ury instructions as to the meaning of the limitations of the claims of the '332 patent).
Trial Transcript from Dec. 11, 2000 at 2817-22 (reading of jury verdict).
Jury verdict, dated Dec. 11, 2000.
D.I. 699, Motion by Defendant BSC and Scimed Life Systems, Inc. For Summary Judgment of Invalidity of U.S. Appl. No. 5,902,332 dated Apr. 4, 2000.
D.I.896, Order Denying Motion for Summary Judgment of Invalidity and Unenforceability of Claims 1, 2, and 5 of the U.S. Appl. No. 5,902,332 Denying {699-1} Motion for Summary Judgment of Invalidity of U.S. Appl. No. 5,902,332 dated Oct. 12, 2000.
Wright et al., Percutaneous Endovascular Stent: An Experimental Study (Abstract), RSNA Meeting (Nov. 28, 1984).
Hearing Transcript from Feb. 10, 1998 at 122-32, 146-80 (Attorneys' opening remarks regarding '417 patent); 180-312 (R. Schatz testimony) [Portions of This Transcript Have Been Removed as Confidential].
Hearing Transcript from Feb. 11, 1998 at 427-575, 577-651 (Cordis expert testimony regarding the '417 patent, the prior art and the Palmaz-Schatz stent).
Hearing Transcript from Feb. 13, 1998 at 1121-1261 (Guidant expert testimony regarding the alleged obviousness of the '417 patent, the prior art and the Palmaz-Schatz stent). [Portions of This Transcript Have Been Removed as Confidential].
Order by J. Robinson denying Cordis' Motion for a Preliminary Injunction Against ACS dated Jul. 17, 1998.
ACS, Inc.'s and Guidant Corp.'s Opening Brief in Support of Their Motion for Summary Judgment of Invalidity of U.S. Appl. No. 5,102, 417 dated Aug. 27, 1998.
Plaintiffs's Answering Brief in Opposition to ACS' and BSC's Motion for Summary Judgment on Obviousness dated Sep. 24, 1998.
Order dated Mar. 31, 2000.
Schatz Deposition Testimony; May 15, 1996: 79-83, 89-92, 105-107 and 153-161.
Schatz Deposition Testimony; May 16, 1996: 555-564, 569-572.
Schatz Deposition Testimony; Jan. 8, 1998: 67-73, 108-110.
Schatz Deposition Testimony; Jul. 14, 1998: 69-77, 108-112, 119-123.
Schatz Deposition Testimony; Jul. 12, 1999: 88-91, 132-135, 144-149, 218-223, 231-242.
Schatz Deposition Testimony; Jul. 13, 1999: 251-334, 339-345, 374-416.
Schatz Deposition Testimony; Jul. 14, 1999: 454-550.
Schatz Deposition Testimony; Jul. 15, 1999: 560-614.
Schatz Deposition Testimony; Dec. 2, 1999: 906-91 1, 928-942, 945-963, 976-978, 1029-1034, 1038-1042.
Palmaz Deposition Testimony, Nov. 5, 1991: 160-172.
Palmaz Deposition Testimony, Feb. 5, 1995: 710-727.
Palmaz Deposition Testimony, Jul. 16, 1998: 55-56; 81-82.
Palmaz Deposition Testimony, Jul. 28, 1999: 560-568, 570-579.
Palmaz Deposition Testimony, Jul. 29, 1999: 778-785.
Palmaz Deposition Testimony, Aug. 31, 1999: 1403-1452.
Palmaz Deposition Testimony, Sep. 2, 1999: 1953-1960.
Palmaz Deposition Testimony, Oct. 14, 1999: 2201-2209; 2275-2342; 2371-2411.
Palmaz Deposition Testimony, Oct. 15, 1999: 2424-2497; 2508-2589.
Palmaz Deposition Testimony, Oct. 16, 1999: 2853-2860.
Tobor Deposition Testimony, Jun. 17, 1999: 837-958.
Tobor Deposition Testimony, Jun. 18, 1999: 1095-1184.
Tobor Deposition Testimony, Dec. 1, 1999: 1217-1371.

Tobor Deposition Testimony, Dec. 2, 1999: 1398-1414; 1444-1508; 1532-1548.
Tobor Deposition Testimony, Dec. 3, 1999: 1652-1653; 1662-1672; 1683-1694.
Kula Deposition Testimony, Apr. 20, 1999: 268-169.
Kula Deposition Testimony, Nov. 16, 1999: 660-675; 680-694; 7-8-755; 774-821.
Kula Deposition Testimony, Nov. 18, 1999; 176-223.
Expert Report of Dr. Rodney S. Badger on Behalf of Medtronic AVE, Inc. (Jan. 31, 2000).
Expert Report of Dr. Joseph Bonn on Behalf of Medtronic AVE, Inc. (Jan. 31, 2000).
Deposition of Dr. Joseph Bonn dated Mar. 14, 2000.
Rebuttal Expert Report of Nigel Buller, B.Sc., M.B., F.R.C.P. (Mar. 2000).
Second Supplemental Rebuttal Expert Report of Nigel Buller, B.Sc., M.B., F.R.C.P. (Aug. 17, 2004).
Rebuttal Expert Report of John M. Collins, PH.D. (Feb. 2000).
Expert Report of David C. Cumberland, M.D. (Jan. 24, 2000).
Expert Report of John T. Goolkasian (Feb. 2000).
Deposition of Richard R. Heuser, M.D. (Sep. 7, 2004).
Deposition of Henry R. Piehler (Sep. 10, 2004).
Deposition of Ronald J. Solar (Mar. 22, 2000).
Deposition of Ronald J. Solar (Mar. 23, 2000).
Deposition of Ronald J. Solar (Apr. 12, 2000).
Expert Report of Dr. Arina Van Breda on Behalf of Medtronic AVE, Inc. (Jan. 31, 2000).
Deposition of Anna Van Breda (Mar. 24, 2000).
Deposition of Arina Van Breda (Aug. 21, 2004).
Expert Report of John F. Witherspoon (Jan. 24, 2000).
Supplemental Expert Report of John F. Witherspoon (Oct. 27, 2000).
Deposition of John F. Witherspoon (Mar. 8, 2000).
Palmaz et al., Article: "Normal and Stenotic Renal Arteries: Experimental Balloon Expandable Intraluminal Stentintg", Radiology, Sep. 1987. (AVE 84).
Julio C. Palmaz, Article: "Expandable vascular endoprosthesis." (AVE 132).
Duprat et. al., Article: Flexible Balloon-Expandable Stent for Small Vessels Duprat et. al. Radiology, vol. 162, pp. 276-278, 1987. (AVE 134).
Coons et. al., Article: "Large-Bore, Long Biliary Endoprosthesis (Billiary Stents) for Improved Drainage," Radiology, vol. 148, pp. 89-94, 1983. (AVE 143).
Honickman et al., Article: "Malpositioned Biliary Endoprosthesis, Technical Developments And Instrumentation," vol. 144, No. 2., 1982. (AVE 144).
Harries-Jones, et al., Article: "Repositioning of Biliary Endoprosthesis with Gruntzig Balloon Catheters," AJR, vol. 138, pp. 771-772, 1982. (AVE 153).
Charnsangavej et al., Article "Stenosis of the Vena Cava: Preliminary Assessment of Treatment with Expandable Metallic Stents," Radiology, vol. 161, pp. 295-298, 1986. (AVE 359).
Wallace, M. J. et al., Article "Tracheobronchial Tree: Expandable Metallic Stents Used in Experimental and Clinical Applications," Radiology, vol. 158, pp. 309-312, 1986. (AVE 364).
T. Yoshioka, et al., AIR Article: "Self-Expanding Endovascular Graft: An Experimental Study in Dogs", vol. 151, pp. 673-676, 1988. (AVE 438).
Palmaz, J. C. et al., Article: "Expandable Intraluminal Vascular Graft: A Feasibility Study," Surgery, vol. 99, pp. 199-205, 1986. (AVE 461).
Lawrence et al., Article: "Percutaneous Endovescular Graft: Experimental Evaluation." Radiology, vol. 163, pp. 357-360, 1987. (AVE 671).
Palmaz et al., Article: Expandable Intraluminal Graft: A Preliminary Study, Nov. 17-22, 1985, Radiology, vol. 156, pp. 73-77, 1985. (AVE 1224).
Fallone et al., "Elastic Characteristics of the Self-Expanding Metallic Stents," Investigative Radiology, vol. 23, pp. 370-376, 1988. (AVE 1953).
Palmaz Paper Entitled "Research Project Expandable Vascular Endoprosthesis" May 18, 1983.
Rousseau , et al., Publication: "Percutaneous Vascular Stent: Experimental Studies & Preliminary Clinical Results in Peripheral Arterial Diseases," in Inter. Angio, vol. 6, 153-161, 1987. (AVE 3301).
Rousseau , et al., Publication: "Self-Expanding Endovascular Prostesis: An Experimental Study," Radiology, vol. 164, pp. 709-714, 1987. (AVE 3303).
Wallace, et al., Article: "Tracheobronchial Tree: Expandable Metallic Stents Used in Experimental and Clinical Applications," Radiology, vol. 58, pp. 309-312, 1986. (DBX 2938).
Palmaz et al., Article: "Expandable Intraluminal Graft: A Preliminary Study," Radiology, vol. 156, pp. 73-77, Nov. 17-22, 1985 (DBX 4595).
Program for the 12th Annual Course on Diagnostic Angiography and Interventional Radiology Mar. 23-26, 1987 sponsored by The Society of Cardovascular and Interventional Radiology (DBX 6235).
Preliminary Motion for Judgment re: Wolff claims 1, 2-8, 10, 15 and 19 (DBX6759).
Palmaz Declaration (DBX 7069).
Letter from Gaterud to Dr. Palmaz dated Jul. 5, 1988 with attached document entitled: "Segmented, balloon-expandable stents." (DBX 7160).
Duprat et al., Article: "Flexible Balloon-Expandable Stent For Small Vessels," Radiology, vol. 168, pp. 276-278, 1987 (PX 82).
Drawing Sent to Bodic on Mar. 17, 1986 (PX 374).
Letter from Dr. Palmaz to R. Bowman enclosing a model of the flexible coronary graft dated Mar. 17, 1986 (PX 337).
Lab Notebook pages dated Jul. 30, 1987 from Rodney Wolff (COR 185596-597) (PX621A).
Charnsangavej, et al., Article: "Stenosis of The Vena Cava Prelimimnary Assessment of Treatment with expandable Metallic Stents," Radiology, vol. 161, No. 2, pp. 295-298 with attached photographs, 1986. (API 72).
J. Palmaz: The Current Status of Vascular Prosthesis, published by SCIR in the Twelfth Annual Course on Diagnostic Angiography And Interventional Radiology Mar. 23-26, 1987. (API 73).
Amendment in Response to Office Action of Oct. 18, 1998 in re: Application of Julio Palmaz U.S. Appl. No. 174,246. (API 152).
Article: Wallace, et al., Tracheobroncial Tree: Expandable Metallic Stents Used in Experimental and Clinical Applications Work In Progress, Radiology, vol. 158, pp. 309-312. (API 295).
Reply of Senior Party Schatz To Patentee Wolffs Opposition To The Belated Motion For Judgment Of Applicant Schatz With Regard To Wolff Claims 1, 2-8, 10, 1 1, 13-17, And 19 (COR 186450-455) (API 310).
Brief Of Senior Party Schatz At Final Hearing (API 313).
Copy of Letter from Ron Sickles to Ben Tobor dated Feb. 10, 1988 (Exhibit 42).
Copy of Letter from R.O. Sickles to Mike Tatlow dated May 12, 1988 (Exhibit 43).
Copy of Letter from R. 0. Sickles to Richard Schatz dated Jun. 2, 1988 (Exhibit 44).
Copy of Letter from Richard Schatz to Raimund Erbel dated Jun. 3, 1988 (Exhibit 45).
Copy of Letter from Richard Schatz to Mike Schuler dated Aug. 29, 1991 (Exhibit 48).
Minutes of J&J Stent Project Review Meeting datd Jan. 21, 1988 (Exhibit 7).
Preliminary Motion for Judgment with Regard to Wolff Claims 1, 2-8, 10, 11, 13-17, and 19. (Exhibit 67).
Declaration of Richard A Schatz. (Exhibit 75).
Belated Motion for Judgement with Regard to Wolff Claims 1, 2-8, 10, 1 1, 13-17 and 19. (Schatz—Exhibit 77).
Letter from Dr. Schatz to Mr. Tobor, dated Jun. 3, 1988. (Exhibit 122).
Letter from Dr. Schatz to Mr. Romano, dated Nov. 28, 1988. (Exhibit 131).
Letter from Mr. Sickles to Mr. Tobor, dated Feb. 10, 1988 (Exhibit 145).
Richard A. Schatz, Article title: "A View of Vascular Stents" Circulation, vol. 79, No. 2, pp. 445-457, 1989. (Exibit 194).

Senior Party Schatz's reply to Patentee Wolffs Opposition to the Preliminary Motion Of Application Schatz for judgment with regard to Wolff Claims 1, 2-8, 10, 1 1 , and 13-17. (Exhibit 69).
Wallace, et al., Article: " Tracheobronchial Tree: Expandable Metallic Stents Used in Experimental and Clinical Applications' Work In Progress," Radiology, vol. 158, pp. 309-312, 1986. (Exhibit 165).
Charnsangavej, et al., Article: "Stenosis of The Vena Cava Prelimimnary Assessment of Treatment with expandable Metallic Stents," Radiology, vol. 161, No. 2, pp. 295-298 with attached photographs, 1986! (Exhibit 167).
David D. Lawrence et al., Publication: Percutaneous Endoyascular Graft: Experimental Evaluation[1], Radiology, pp. 163, 357-360, 1987. (Exhibit 173).
Charles E. Putnam, M.D., Cover and article from "Investigative Radiology", vol. 23, No. 5, May 1988. (Exhibit 177).
Robert N. Berk, Cover and article from "American Journal of Roentology", pp. 673-676, 1988. (Exhibit 178).
Declaration of John S. Kula Under 37 CFR § 1 .672. (Kula—Exhibit 77).
Yoshioka et al., Article: "Self-Expanding Endovascular Graft: An Experimental Study in Dogs" AJR, vol. 151, pp. 673-676, 1988. (PX 100).
Palmaz, et al., Article: Expandable Intraluminal Graft: A Preliminary Study Work in Progress[1], Radiology, vol. 156, No. 1, pp. 73-77, 1985. (PX 101).
Declaration of Richard Schatz Under 37 C.F.R.§ 1.672. (PX 106).
Charnsangavej et al., Article: "Stenosis of the Vena Cave: Preliminary Assessment of Treatment with Expandable Metallic Stents," Radiology, vol. 161, pp. 295-298, 1986. (PX 143).
Wallace, et al., Article: Tracheobronchial Tree: Expandable Metallic Stents Used in Experimental and Clinical Applications Work in Progress[1], Radiology, vol. 158, pp. 309-312, 1986. (PX 144).
Gina Kolata, News Article: NY Times, "Devices That Opens Clogged Arteries Gets a Falling Grade in a New Study", pp. 16-18, Jan. 3, 1991. (PX 186).
Duprat, et al., Article: "Flexible Balloon-Expanded Stent for Small Vessels Work in Progress[1]", Radiology, vol. 162, pp. 276-278, 1987. (PX 207).
Letter from Palmaz to Bowman dated Mar. 17, 1986. (PX 350).
Memo re: Minutes of Stent Project Review- San Antonia- Mar. 15, 1988. (PX 651).
Kuntz, et al., Article: Clinical Cardiology Frontiers: "Defining Coronary Restenosis, Newer Clinical and Angiographic Paradigms", Circulation, Sep. 1993, vol. 88, No. 3, pp. 1310-1323. (PX 854).
Belated Motion for Judgment with regard to Wolff Claims1, 2-8, 10, 11, 13-17, and 19. (PX 1410).
Drawing of Spiral Stent (sent to Bodic Mar. 17, 1986). (PX2933).
Wright et al., Article: "Percutaneous Endovascular Stents: An Experimental Evaluation," Radiology, vol. 156, pp. 69-72, 1985. (PX 3093).
Charnsangavej et al., Article: "A New Expandable Metallic Stent for Dilation of Stenotic Tubular Structures: Experimental and Clinical Evaluation," Houston Medical Journal, vol. 3, pp. 41-51, Jun. 1987. (PX 3207).
In re Application of Wiktor, U.S. Appl. No. 69,636, Response to Office Action dated Mar. 17, 1988. (PX3236).
Transmittal Letter of Response to First Office Action in '417 patent. (PX 3993).
Letter from B. Tobor to R. Schatz dated Jul. 23, 1991. (PX 3996).
Mullins et al., Article: "Implantation of balloon-expandable intravascular grafts by catherization in pulmonary arteries and systemic veins," Circulation, vol. 77, No. 1, pp. 188-189, 1988. (PX4049).
Schatz et al., Article: "Intravascular Stents for Angioplasty," Cardio, 1997. (PX 4050).
Schatz et al., Article: "New Technology in Angioplasty Balloon-Expandable Intravascular Stents, New Developments in Medicine," vol. 2, No. 2, pp. 59-75, 1987. (PX405I).
Richard A. Schatz, Article: "Introduction to Intravascular Stents," Cardiology Clinics, vol. 6, No. 3, pp. 357-372, 1988. (PX 4052).
Richard A. Schatz, Article: "A View of Vascular Stents," Circulation, vol. 79, No. 2, pp. 445-457, 1989. (PX4053).
Wang et al., Article: "An Update on Coronary Stents," Cardio, pp. 177-186, 1992. (PX 4054).
Richard A. Schatz, Article: "New Technology in Angioplasty: Balloon-Expandable Starts," Medicamundi, vol. 33, No. 3, pp. 1 121-1 16, 1988. (PX 4055).
Letter from Tobor to Schatz dated Sep. 29, 1988. (PX 1395).
Verified Statement of Facts by Innamed Inventor R.A. Schatz document filed in U.S. Patent and Tradement Office on Sep. 8, 1989. (PX 3677).
Declaration of John S. Kula Under 37 CFR § 1.672 (Exhibit 329).
Letter to Mike Schular from R.A. Schatz dated Aug. 29, 1991. (Exhibit 402).
Articulated, Balloon—Expandable Stents, (DBX 7159).
J. Rosch et al., Experimental Intrahepatic Portacaval Anastomosis: Use of Expandable Gianturco Stents, Radiology, vol. 162, pp. 481-485, 1987.
J. Rosch et al., Modified Gianturco Expandable Wire Stents In Experimental and Clinical Use, Ann Radiol, vol. 31, No. 2, pp. 100-103, 1987.
J. Rosch et al., Gianturco Expandable Stents In the Treatment of Superior Vena Cava Syndrome Recurring After Vena Cava Syndrome Recurring After Maximum-Tolerance Radiation, Cancer, vol. 60, pp. 1243-1246, 1987.
I.E. Gordon, Structures or Why Things Don't Fall Down, Penguin Books, pp. 45-59,132-148,210-244,377-383.
Maass et al., Radiological Follow-up of Transluminally Inserted Vascular Endoprostheses: An Experimental Study Using Expanding Spirals, Radiology, vol. 152, pp. 659-663, 1984.
Argument submitted re EP 861 15473 dated Jan. 20, 1995. (AVE 2478).
Verified Statement of Facts by Julio C. Palmaz dated Aug. 4, 1989. (PX 3662).
Papanicolaou et al., Insertion of a Biliary Endoprosthesis Using A Balloon Dilatation Catheter, Gastrointest Radiology, vol. 10, pp. 394-396, 1985.
Palmaz et al., Atheroscierotic Rabbit Aortas: Expandable Intraluminal Grafting, Radiology, vol. 168, pp. 723-726, 1986.
Palmaz, The Current Status of Vascular Prostheses; Rosch et al., Gianturco, Expandable Stents in Experimental and Clinical Use, SCIVR, pp. 1 18-124, 1987.
Rosch et al., Abstract: Modified Gianturco Expandable Wire Stents in Experimental and Clinical Use, CIRSE, Porto Cervo, Sardinia, May 25-29, 1987.
Rosch et al., Gianturco Expandable Wire Stents in the Treatment of Superior Vena Cava Syndrome Recurring After Maximum-Tolerance Radiation, Cancer, vol. 60, pp. 1243-1246, 1987.
Mirich et al., Percutaneously Placed Endovascular Grafts for Aortic Aneurysms: Feasibility Study, Radiology, vol. 170, pp. 1033-1037, 1989.
Dotter, Transluminally-placed Coilspring Endarterial Tube Grafts, Investigative Radiology, vol. 4, Sep.-Oct., pp. 329-332, 1969.
Palmaz et al., Abstract: Expandable Intraluminal Graft: A Preliminary Study, Radiology, vol. 153 (P), Nov. 1983: 70th Scientific Assembly and Annual Meeting.
Cragg et al, Nonsurgical Placement of Arterial Endoprosthesis: A New Technique Using Nitinol Wire, Radiology, vol. 147, pp. 261-263, Apr. 1983.
J. Rosch et al., Gianturco Expandable Stents in Experimental and Clinical Use, Program: "Twelfth Annual Course on Diagnostic Angiography and Interventional Radiology" (Society of Cardiovascular and Interventional Radiology, Pittsburgh, PA), Mar. 23-26, 1987 (the second Monofilament Article).
Uchida t al., Modifications of Gianturco Expandable Wire Stents, AIR, vol. 150, pp. 1185-1187, 1988.
Palmaz, Balloon-Expandable Intravascular Stent, AJR, vol. 1510, pp. 1263-1269.
Cordis Corporation v. Advanced Cardiovascular Systems, Inc., Guidant Corporation, Arterial Vascular Engineering, Inc., Boston Scienctific Corporation and SCMED Life Systems, Inc., Plaintiffs Complaint, Oct. 23, 1997 (Case No. 97-550-SLR).
Arterial Vascular Engineering, Inc. v. Cordis Corporation, Johnson & Johnson and Expandable-Grafts Partnership, Plaintiffs First Amended Complaint for Declaratory Relief of Patent Validity,

Unenforceability, Noninfiingement, and for Antitrust Violations, Jan. 27, 1998 (Civil Action No. 97-700).
Arterial Vascular Engineering, Inc. v. Cordis Corporation, Johnson & Johnson and Expandable-Grafts Partnership, Cordis Corporation and Johnson & Johnson's Answer and Counterclaim, Feb. 27, 1998 (Civil Action No. 97-700-SLR).
Arterial Vascular Engineering, Inc. v. Cordis Corporation, Johnson & Johnson and Expandable-Grafts Partnership, Expandable-Graft Partnership's Answer, Feb. 27, 1998 (Civil Action No. 97-700-SLR).
Arterial Vascular Engineering, Inc. v. Cordis Corporation, Johnson & Johnson and Expandable-Grafts Partnership, Reply of Plaintiff Arterial Vascular Engineering, Inc. To Counterclaims of Defendant Cordis Corporation, Mar. 31, 1998 (Civil Action No. 97-700-SLR).
Arterial Vascular Engineering, Inc. v. Cordis Corporation, Johnson & Johnson and Expandable-Grafts Partnership, Reply of Plaintiff Arterial Vascular Engineering, Inc. To Counterclaims of Defendant Expandable Grafts Partnership, Mar. 31, 1998 (Civil Action No. 97-700-SLR).
Cordis Corporation v. Advanced Cardiovascular Systems, Inc. and Guidant Corporation, Cordis Corporation's Motion for a Preliminary Injunction, Oct. 8, 1997 (Civil Action No. 97-550.).
Cordis Corporation v. Advanced Cardiovascular Systems, Inc., Guidant Corporation Arterial Vascular Engineering, Inc., Boston Scientific Corporation and SCJJVIED, Inc., Cordis 's Motion for Preliminary Injunction Against Arterial Vascular Engineering, Inc., Dec. 29, 1997 (Case No. 97-550-SLR).
Deposition of R. Schatz, M.D. in Cordis Corporation v. Advanced Cardiovascular Systems, Inc., taken on Jan. 8, 1998 (Civil Action No. 97-550 SLR).
Deposition of Lee P. Bendel in Cordis Corporation v. Advanced Cardiovascular Systems, Inc., taken on Jan. 22, 1998 (Civil Action No. 97-550 SLR).
Deposition of Julio Cesar Palmaz in Cordis Corporation v. Advanced Cardiovascular Systems, Inc., taken on Dec. 29, 1997 (Civil Action No. 97-550 SLR).
Deposition of Richard A. Bowman in Cordis Corporation v. Advanced Cardiovascular Systems, Inc., taken on Jan. 9, 1998 (Civil Action No. 97-550 SLR).
Deposition of Gary Schneiderman in Cordis Corporation v. Advanced Cardiovascular Systems, Inc., taken on Jan. 16, 1998 (Civil Action No. 97-550 SLR).
Deposition of David Pearle, M.D. in Cordis Corporation v. Advanced Cardiosvascular Systems, Inc., taken on Jul. 10, 1998 (Civil Action No. 97-550 SLR).
Preliminary Injunction hearing testimony taken on Feb. 9-13, 1998 (Civil Action No. 97-550 SLR).
Cordis Corporation v. Advanced Cardiovascular Systems, Inc., et al., (Civil Action No. 97-550 SLR) and Cordis Corporation v. Advanced Cardiovascular Systems, Inc. Et al. (Civil Action No. 98-65-SLR), Opening Post Hearing Brief of Plaintiff Cordis Corporation in Support of Motion for Preliminary Injunction, Mar. 6, 1998 (Portions relevant to patent claim construction and patent validity issues).
Cordis Corporation and Expandable Grafts Partnership v. Advanced Cardiovascular Systems, Inc. et al., Post-Hearing Reply Brief of Plaintiff Cordis Corporation in Support of Its Motion for Preliminary Injunction, Apr. 10, 1998 (Case No. 97-550 SLR) (Portions relevant to patent validity issues).
Cordis Corporation and Expandable Grafts Partnership v. Advanced Cardiovascular Systems, Inc. et al., Plaintiffs Motion for a Preliminary Injunction Against Boston Scientific Corporation and SCLMED Life Systems, Inc. And Memorandum in Support, Apr. 13, 1998 (Case No. 97-550-SLR).
Cordis Corporation and Expandable Grafts Partnership v. Advanced Cardiovascular Systems, Inc., et al., Judge Robinson's Order Denying Plaintiffs Motion for a Preliminary Injunction, Jul. 17, 1998 (Civil Action No. 97-550 SLR).
Cordis Corporation and Expandable Grafts Partnership v. Advanced Cardiovascular Systems, Inc., et al., Defendant Boston Scientific Corporation and SCTMED Life Systems, Inc.'s Motion for Summary Judgment of Invalidity of U.S. Appl. No. 5,102,417, Aug. 27, 1998 (Civil Action No. 97-550-SLR).
Boston Scientific Limited, et al. v. Expandable Grafts Partnership, Plaintiffs' Statement of Claim, Mar. 13, 1997 (UK Action No. 1493).
Boston Scientific Limited, et al: v. Expandable Grafts Partnership, Defendant's Amended Defense and Counterclaim, Aug. 14, 1997 (UK Action No. 1493).
Boston Scientific Limited, et al. v. Expandable Grafts Partnership, Petition for Revocation, Mar. 13, 1997 (UK Action No. 1497).
Boston Scientific Limited, et al. v. Expandable Grafts Partnership, Particulars of Objections, Mar. 13, 1997 (UK Action No. 1497).
Boston Scientific Limited, et al. v. Expandable Grafts Partnership and Boston Scientific Limited et al., v. Julio C. Palmaz, Boston's Skeleton Argument (UK Action Nos. 1493, 1495, 1496, and 1497).
Boston Scientific Limited, et al. v. Julio C. Palmaz and Expandable Grafts Partnership, Skeleton Argument of Palmaz/EGP, Mar. 19, 1998 (UK Action Nos. 1493, 1495, 1496 and 1497).
Boston Scientific Limited, et al. v. Julio C. Palmaz and Expandable Grafts Partnership, EGP's Final Submissions, Apr. 2, 1998 (UK Action Nos. 1493, 1495, 1496 and 1497).
Boston Scientific Limited, et al. v. Julio C. Palmaz and Expandable Grafts Partnership, Judgment, Jun. 26, 1998 (UK Action Nos. 1493, 1495, 1496 and 1497).
Rosch, Modified Gianturco Expandable Wire Stents in Experimental and Clinical Use, CJJR.SE 1987 Presentation: see Witness Statement of Josef Rosch from U.K. Proceeding.
Statement of Claim by Boston Scientific et al. against Expandable Grafts Partnership et al., in EPG et al., v. Boston Scientific et al. in Netherlands (Mar. 13, 1997).
Motion for Joinder of Actions, Change of Claim and Statement of Claim filed by Expandable Grafts Partnership et al. in EPG et al. v. Boston Scientific et al. In Netherlands (Apr. 22, 1997).
Opinion of K.J. Merman filed in EPG et al. v. Boston Scientific et al. in Netherlands (Aug. 29, 1997).
Expert report of Dr. Nigel Buller in EPG et al. v. Boston Scientific et al. in Netherlands (Aug. 28, 1997).
Expert report of Lee P. Bendel in EPG et al. v. Boston Scientific et al. in Netherlands (Aug. 28, 1997).
Memorandum of Oral Pleading in EPG et al. v. Boston Scientific et al. in Netherlands (Sep. 12, 1997).
Plea Notes of P. A.M. in EPG et al. v. Boston Scientific et al. in Netherlands (Mar. 10, 1998).
Decision of Court of Appeals in EPG et al. v. Boston Scientific et al. in Netherlands (Apr. 23, 1998).
Translation of Nullity Action Against EPO 0 364 787 by Biotronik in Germany.
Translation of Nullity Action Against EPO 0 335 341 by Biotronik in Germany.
Translation of EPG Response to Nullity Action Against EP 0 364 787 by Biotronik in Germany.
Translation of EPG Response to Nullity Action EP 0 335 341 by Biotronik in Germany.
Nullity Suit Against EP-B1-0 335 341 Brought by Boston Scientific in Germany.
Translation of Opposition filed by Terumo Corp. Against Japan Patent No. 2680901.
Translation of Decision on Opposition Against Japan Patent No. 2680901.
Memorandum Order of the Court dated Sep. 7, 2000, concerning disputed claim construction.
Translation of Judgment in Nullity Action Against EP 0 364 787 by Biotronik in Germany.
Translation of Judgment in Nullity Action Against EP 0 335 341 by Biotronik in Germany.
Trial transcript from Mar. 17, 2005 at 171-172, 191-192.
Trial transcript from Mar. 18, 2005 at 282-285, 325-327, 349-351.
Trial transcript from Mar. 21, 2005 at 721-726.
Trial transcript from Mar. 24, 2005 at 1387.
Trial transcript from Jul. 26, 2005.
BSC's Opening Brief in Support of Its Motion for Judgment as a Matter of Law or, in the Alternative, for a New Trial, dated Mar. 16, 2001.

Cordis' Answering Brief in Opposition to BSC's Motion for JMOL or a New Trial on the Palmaz '762 Patent and the Schatz '332 Patents, dated Apr. 17, 2001.

BSC's Reply Brief in Support of Its Motion for Judgment as a Matter of Law or, in the Alternative, for a New Trial, dated May 11, 2001.

J. Rosch et al., Abstract, Expandable Gianturco-Type Wire Stents in Experimental Intrahepatic Portacaval Shunts, Program: "72nd Scientific Assembly and Annual Meeting of the Radiological Society of North America", Nov. 30-Dec. 5, 1986m Radiology, vol. 161, pp. 40-41, 1986.

Cordis Corporation v. Boston Scientific, Order Dated Mar. 27, 2006 (97-550-SLR).

Cordis Corporation v. Boston Scientific, Judgment in a Civil Case Dated Mar. 27, 2006 (97-550-SLR).

Cordis Corporation v. Boston Scientific, Memorandum Opinion Dated Mar. 27, 2006 (97-550-SLR).

Cordis Corporation and Expandable Grafts Partnership v. *Advanced Cardiovascular Systems, Inc., Guidant Corporation, Arterial Vascular Engineering, Inc., Boston Scientific Corporation and SCIMED Life Systems, Inc.*, Answer and Counterclaims of Defendant Advanced Cardiovascular Systems, Inc., Apr. 8, 1998 (Case No. 97-550-SLR).

Boston Scientific Limited et al. v. *Expandable Grafts Partnership and Boston Scientific Limited et al.* v. *Julio C. Palmaz*, Boston's Closing Submissions (UK Action Nos. 1493, 1495, 1496 and 1497).

Cordis Corporation v. *Advanced Cardiovascular Systems, Inc., Guidant Corporation, Arterial Vascular Engineering, Inc., Boston Scientific Corporation and SCIMED Life Systems, Inc.*, Defendants' Answer, Nov. 12, 1997 (Case No. 97-550-SLR).

Statement of Rejoinder in the Action on the Merits, Also Including an Amendment of Defendant's Final Position in the Principal Action, as Well as the Provisional Statement of Rejoinder in the Action on the Counterclaim in *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Feb. 10, 1998).

Statement of Answer in the Ancillary Appeal in *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Mar. 10, 1998).

Appeal filed by Expandable Grafts Partnership et al. in *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Nov. 12, 1997).

Title filed by Boston Scientific et al. in *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Jan. 22, 1998).

Deposition of Richard Schatz, M.D. in *Cordis Corporation* v. *Advanced Cardiovascular Systems, Inc.* taken on Jul. 14, 1998 (Civil Action No. 97-550-SLR).

Jury Verdict form from the *Cordis Corporation et al* v. *Boston Scientific Corporation, et al* liability trial, undated.

Trial testimony transcripts from the *Cordis Corporation et al.* v. *Boston Scientific Corporation et al.* liability trial dated Nov. 21, Nov. 27-Dec. 1, Dec. 4-8 and Dec. 11, 2000.

Boston Scientic SCIMED, Inc. and Boston Scientific Corporation v. *Cordis Corporation and Johnson and Johnson, Inc.*, Opening Expert Report of Stephen R. Hanson, Ph.D. (Civil Action No. 03-328-SLR).

Boston Scientific SCIMED, Inc. and Boston Scientific Corporation v. *Cordis Corporation and Johnson and Johnson, Inc.*, Opening Expert Report of Robson F. Storey, Ph.D. (Civil Action No. 03-283-SLR).

Boston Scientific SCIMED, Inc. and Boston Scientific Corporation v. *Cordis Corporation and Johnson and Johnson, Inc.*, Rebuttal Expert Report of Kinam Park, Ph.D. (Civil Action No. 03-283-SLR).

Cordis Corporation v. *Boston Scientific Corporation and SCIMED Life Systems, Inc.* (C.A. No. 03-027-SLR) and *Boston Scientific SCIMED, Inc., and Boston Scientific Corporation* v. *Cordis Corporation and Johnson and Johnson, Inc.* (C.A. No. 03-283-SLR) Combined Post-Hearing Brief In Support Of Cordis Corporation's Motion For Preliminary Injunction in C.A. No. 03-027-SLR, And In Opposition to Plaintiffs' Motion For Preliinary Injunction in C.A. No. 03-283-SLR.

Cordis Corporation v. *Boston Scientific Corporation and SCIMED Life Systems, Inc.* (C.A. No. 03-027-SLR) *Boston Scientific SCIMED, Inc., and Boston Scientific Corporation* v. *Cordis Corporation and Johnson and Johnson, Inc.* (C.A. No. 03-283-SLR), Boston Scientific's Opening Post-Hearing Brief.

Cordis Corporation v. *Boston Scientific Corporation and SCIMED Life Systems, Inc.* (C.A. No. 03-027-SLR) *Boston Scientific SCIMED, Inc., and Boston Scientific Corporation* v. *Cordis Corporation and Johnson and Johnson, Inc.* (C.A. No. 03-283-SLR), Combined Post-Hearing Answering Brief In Support of Cordis Corporation's Motion For Preliminary Injunction In C.A. No. 03-027-SLR, And In Opposition To Plaintiffs Motion For Preliminary Injunction in C.A. No. 03-283-SLR.

Wu et al., Silicone-covered self-expanding metallic stents for the palliation of malignant esophageal obstruction and esophagorespiratory fistulas: experience in 32 patients adn a review of the literature, *Gastrointestinal Endoscopy*, 1994, pp. 22-33, vol. 40, No. 1, Portland Oregon.

Binmoeller, et al., Silicone-Covered Expandable Metallic Stents in the Esophagus: An Experimental Study, Endoscopy, 1992, pp. 416-420, vol. 24, Georg Thieme Verlag Stuttgart New York.

Boston Scientific SCIMED, Inc., and Boston Scientific Corporation v. *Cordis Corporation and Johnson and Johnson, Inc.*, Answering Memorandum in Opposition to Plaintiffs Motion for a Preliminary Injunction and Appendix thereto (Civil Action No. 03-283-SLR).

Boston Scientific SCIMED, Inc., and Boston Scientific Corporation v. *Cordis Corporation and Johnson and Johnson, Inc.*, Answering Memorandum in Opposition to Plaintiffs Motion for a Preliminary Injunction and Appendix thereto (Civil Action No. 03-283-SLR).

Rhine, Polymers for Sustained Macromolecule Release: Procedures to Fabricate Reproducible Delivery Systems and Control Release Kinetics, *Journal of Pharmaceutical Sciences*, 1 980, pp. 265-270, vol. 69, No. 3.

Langer et al., Controlled Release of Macromolecules From Polymers, *Biomedical Polymers Polymeric Materials and Pharmaceuticals for Biomedical Use*, 1980, pp. 112-137, Academic Press, Inc., New York, NY.

Langer et al., Applications of Polymeric Delivery Systems for Macromolecules and Factors Controlling Release Kinetics.

Rhine et al., A Method to Achieve Zero-Order Release Kinetics From Polymer Matric Drug Delivery Systems, pp. 67-72.

Langer et al., Polymers for the Sustained Release of Macromolecules: Controlled and Magnetically Modulated Systems, *Better Therapy With Existing Drugs: New Uses and Delivery Systems*; 1981, pp. 179-216, Merck Sharp & Dohme International, Rahway, NJ.

Hsieh, et al., Zero-Order Controlled-Release Polymer Matrices for Micro-and-Macromolecules, *Journal of Pharmaceutical Sciences*, 1983 pp. 17-22, vol. 72, No. 1.

Brown et al., In Vivo and In Vitro Release of Macromolecules from Polymeric Drug Delivery Systems, *Journal of Pharmaceutical Sciences*, 1983, pp. 1181-1185, vol. 72, No. 10.

Langer, Implantable Controlled Release Systems, *Pharmac. Ther.*, 1983, pp. 35-51, vol. 21, printed in Great Britain.

Kost et al., Controlled Release of Bioactive Agents, *Trends in Biotechnology*, 1984, pp. 47-51, vol. 2, No. 2, Elsevier BV Amsterdam.

Bawa et al., An Explanation for the Controlled Release of Macromolecules from Polymers, *Journal of Controlled Release*, 1985, pp. 259-267, vol. 1 Elsevier Science BV Amsterdam.

Leong et al., Polymeric controlled drug delivery, 1987, pp. 199-233, vol. 1/3, Elsevier Science Publishers BV Amsterdam.

Langer, Polymeric Delivery Systems, *Targeting of Drugs 2 Optimization Strategies*, 1989, pp. 165-174, Plenum Press, New York and London.

Langer, Biomaterials in Controlled Drug Delivery: New Perspective from Biotechnological Advances; *Pharmaceutical Technology*, 1989, pp. 18, 23-24, 26, 28, 30.

Langer, Controlled Release Systems, pp. 115-124.

Laurencin et al., Polymeric Controlled Release Systems: New Methods for Drug Delivery, *Clinics in Laboratory Medicine*, 1987, pp. 301-323, vol. 7, No. 2, WB Saunders Company, Philadelphia.

Langer, Biopolymers in Controlled Release Systems, *Polymeric Biomaterials*, pp. 161-169.

Tsong-Pin Hsu et al., Polymers for the Controlled Release of Macromolecules: Effect of Molecular Weight of Ethylene-vinyl Acetate Copolymer, *Journal of Biomedical Materials Research*, 1985, pp. 445-460, vol. 19.

Langer, Polymers and Drug Delivery Systems, *Long-Acting Contraceptive Delivery Systems*, 1983, pp. 23-32, Harper & Row, Philadelphia, PA.

Langer, New Drug Delivery Systems: What the Clinician Can Expect, *Drug Therapy*, 1983, pp. 217-231.

Langer, et al., Chemical and Physical Structure of Polymers as Carriers for Controlled Release of Bioactive Agents: A Review, *Rev. Macromol. Chem. Phys.*, 1983, pp. 61-126.

Langer, Polymeric Delivery Systems for Controlled Drug Release, *Chem. Eng. Commun.* 1980, pp. 1-48-vol. 6, Gordon and Breach Science Publishers, Inc. USA.

Langer, et al., Biocompatibility of Polymer Delivery Systems for Macomolecules, *Journal of Biomedical Materials Research*, 1981, pp. 267-277, vol. 15.

Langer, Controlled Release: A New Approach to Drug Delivery, *Technology Review*, 1981, pp. 26-34.

Langer, et al., Sustained Release of Macromolecules from Polymers, *Polymeric Delivery Systems*, PGS. 175-176, Gordon adn Breach Science Publishers, New York.

Langer, Polymers for the Sustained Release of Proteins and other Macromolecules, *Nature*, 1976, pp. 797, 263, 799-800, vol. 263, No. 5580.

Baker, et al., Controlled Release: Mechanisms and Rates (1974).

Hanson, et al., In Vivo Evaluation of Artificial Surfaces with a Nonhum Primate Model of Arterial Thrombosis,/ *Lab Clin. Med.*, Feb. 1980, pp. 289-304.

Baker, Controlled Release of Biologically Active Agents (1987) pp. 1-275.

Cordis Corporation v. *Boston Scientific Corporation* (CA. No. 03-27-SLR) and *Boston Scientific Scimed, Inc.*, v. *Cordis Corporation and Johnson & Johnson, Incorporated* (CA. No. 03-283-SLR) Hearing Transcripts for Jul. 21, 2003, Jul. 22, 2003, Jul. 23, 2003.

Cordis Corporation v. *Boston Scientific Corporation et al.* (CA. No. 03-027-SLR), and *Boston Scientific Scimed, Inc. et al.* v. *Cordis Corporation et al.* (CA. No. 03-283-SLR), Boston Scientific's Post-Hearing Reply Brief and Exhibits Thereto, Sep. 12, 2003.

Cordis Corporation v. *Boston Scientific Corporation et al.* (CA. No. 03-027-SLR), and *Boston Scientific Scimed, Inc. et al.* v. *Cordis Corporation et al.* (CA. 03-283-SLR), Memorandum Order, Nov. 21, 2003.

Cordis Corporation v. *Boston Scientific Corporation et al.* (CA. No. 03-027-SLR), and *Boston Scientific Scimed, Inc. et al.* v. *Cordis Corporation et al* (CA. No. 03-283-SLR), Deposition Transcript of Julio C. Palmaz.

Arterial Vascular Engineering, Inc. v. *Cordis Corporation, Johnson & Johnson and Expandable Grafts Partnership*, Cordis Corporation and Johnson & Johnson's Answer and Counterclaim, Feb. 27, 1998 (Civil Action No. 97-700-SLR).

Plea Notes in *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Sep. 12, 1997).

Provisional Judgment *EPG et al.* v. *Boston Scientific et al.* in Netherlands (Oct. 29, 1997).

Trial testimony transcripts from the Cordis Corporation et al. v. Medtronic AVE Inc., et al. liability trial dated Nov. 6-9, 13-17 and 20-21, 2000.

Jury verdict form from the Cordis Corporation et al. v. Medtronic AVE, Inc. et al. liability trial.

Hearing testimony transcript from the consolidated Cordis Corporation et al. v. Medtronic AVE, Inc. et al. and Boston Scientific Corporation et al. inequitable conduct hearing dated Feb. 7-9 and 12, 2001.

Cordis Corporation v. Medtronic Ave., Inc. et al, OPINION, 97-550-SLR, dated Mar. 28, 2002.

Cordis Corporation v. *Advanced Cardiovascular Systems, Inc. et al.* (CA. No. 97-550-SLR), *Medtronic Ave, Inc.* v. *Cordis Corporation et al.* (CA. No. 97-700-SLR), *Boston Scientirfic Corporation* v. *Athicon, Inc. etal.* (CA. No. 98-19-SLR), Expert Report of John T. Goolkasian, Esq.

Cordis Corporation v. *Advanced Cardiovascular Systems, Inc. et al.* (CA. No. 97-550-SLR), *Medtronic A VE, Inc.* v. *Cordis Corporation et al* (CA. No. 97-700-SLR), *Boston Scientific Corporation* v. *Athicon, Inc. et al* (CA. 98-19-SLR), Expert Report of John F. Witherspoon.

"Microbial Conversion of Rapamycin," Kuhnt et al., Enzyme and Microbial Technology, vol. 21, pp. 405-412, 1997.

"Inhibitory Effects of Rapamycin on Intimal Hyperplasia After PTCA," Badimon et al.., JACC, Mar. 1998.

* cited by examiner

FIG. 1

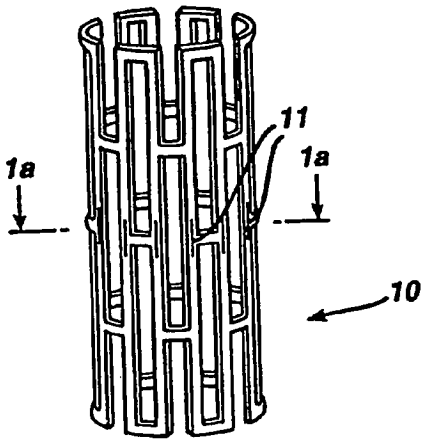


FIG. 1a

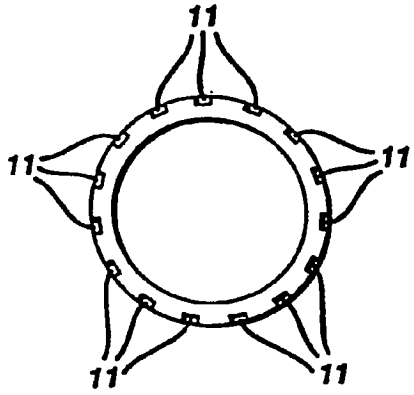


FIG. 2a

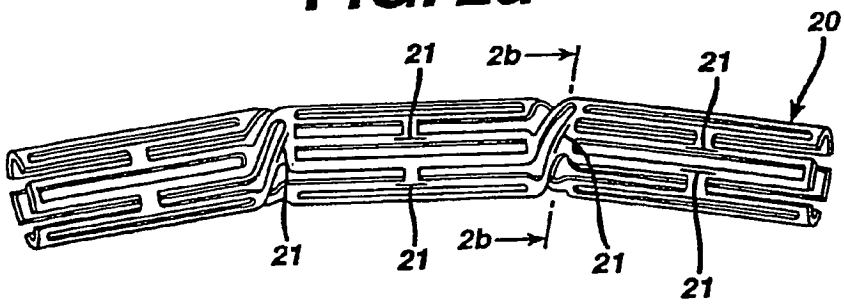


FIG. 2b

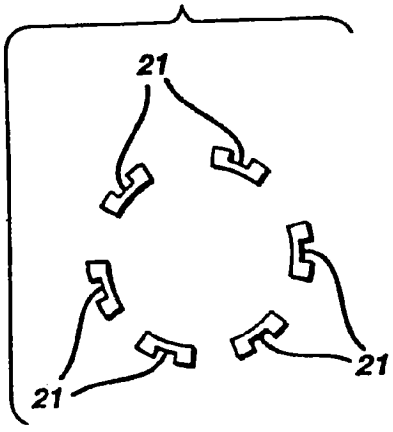


FIG. 3a

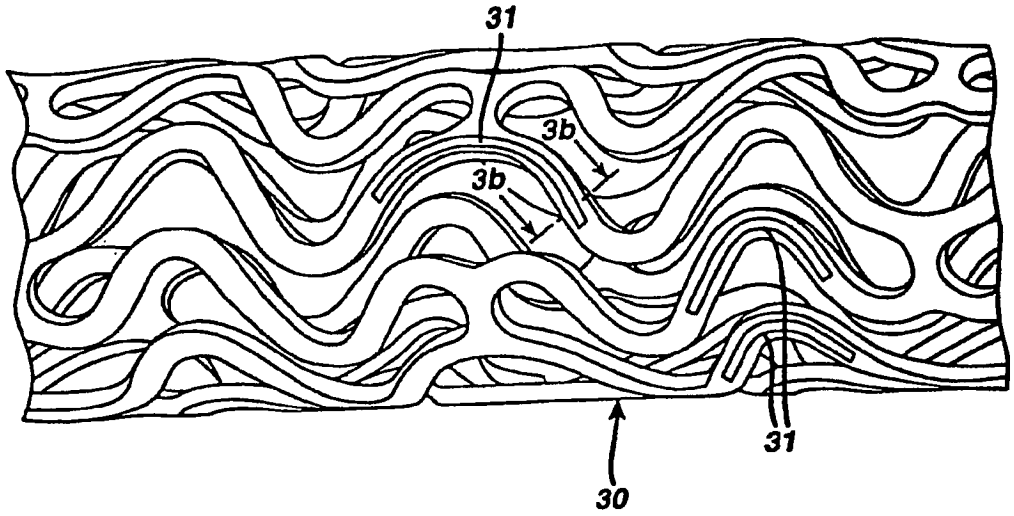


FIG. 3b

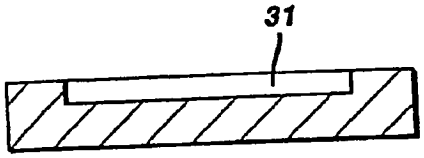
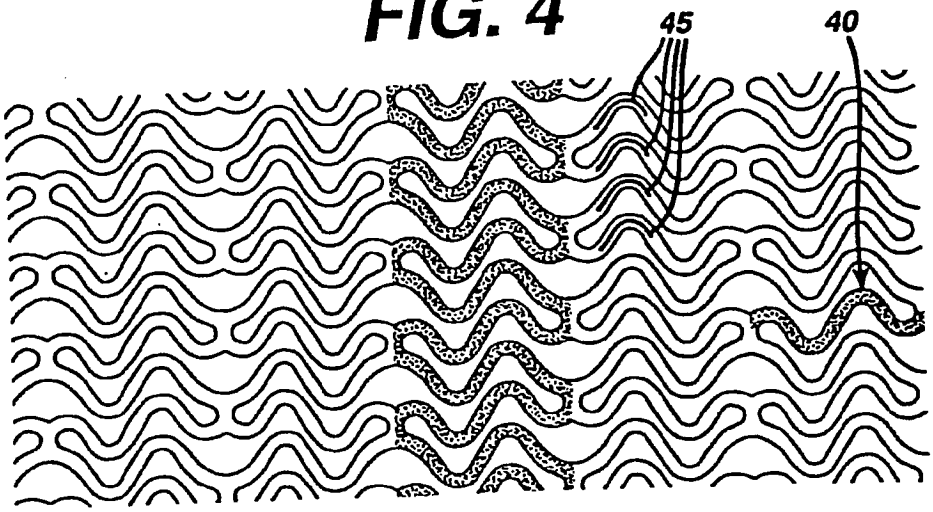


FIG. 4



LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of Ser. No. 10/408,328, filed Apr. 7, 2003, now issued as U.S. Pat. No. 6,808,536, which in turn is a continuation of application Ser. No. 09/874,117, filed Jun. 4, 2001, now issued as U.S. Pat. No. 6,585,764, which is a continuation of application Ser. No. 09/061,568, filed Apr. 16, 1998, now issued as U.S. Pat. No. 6,273,913, which in turn claims benefit of provisional application Ser. No. 60/044,692, filed Apr. 18, 1997.

FIELD OF THE INVENTION

Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

BACKGROUND OF THE INVENTION

Re-narrowing (restenosis) of an artherosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10–50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft. While the exact hormonal and cellular processes promoting restenosis are still being determined, our present understanding is that the process of PTCA, besides opening the artherosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC). In response to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3–6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow.

Several recent experimental approaches to preventing SMC proliferation have shown promise althrough the mechanisms for most agents employed are still unclear. Heparin is the best known and characterized agent causing inhibition of SMC proliferation both in vitro and in animal models of balloon angioplasty-mediated injury. The mechanism of SMC inhibition with heparin is still not known but may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes c-fos and c-myc, 2) reduced cellular production of tissue plasminogen activator; are 3) binding and dequestration of growth regulatory factors such as fibrovalent growth factor (FGF).

Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers, angiotensin converting enzyme inhibitors (captopril, cilazapril), cyclosporin A, trapidil (an antianginal, antiplatelet agent), terbinafine (antifungal),

colchicine and taxol (antitubulin antiproliferatives), and c-myc and c-myb antinsense oligonucleotides.

Additionally, a goat antibody to the SMC mitogen platelet derived growth factor (PDGF) has been shown to be effective in reducing myointimal thickening in a rat model of balloon angioplasty injury, thereby implicating PDGF directly in the etiology of restenosis. Thus, while no therapy has as yet proven successful clinically in preventing restenosis after angioplasty, the in vivo experimental success of several agents known to inhibit SMC growth suggests that these agents as a class have the capacity to prevent clinical restenosis and deserve careful evaluation in humans.

Coronary heart disease is the major cause of death in men over the age of 40 and in women over the age of fifty in the western world. Most coronary artery-related deaths are due to atherosclerosis. Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500,000–600,000 deaths in the United States annually. To arrest the disease process and prevent the more advanced disease states in which the cardiac muscle itself is compromised, direct intervention has been employed via percutaneous transiuminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG)

PTCA is a procedure in which a small balloon-tipped catheter is passed down a narrowed coronary artery and then expanded to re-open the artery. It is currently performed in approximately 250,000–300,000 patients each year. The major advantage of this therapy is that patients in which the procedure is successful need not undergo the more invasive surgical procedure of coronary artery bypass graft. A major difficulty with PTCA is the problem of post-angioplasty closure of the vessel, both immediately after PTCA (acute reocclusion) and in the long term (restenosis).

The mechanism of acute reocclusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus. Recently, intravascular stents have been examined as a means of preventing acute reclosure after PTCA.

Restenosis (chronic reclosure) after angioplasty is a more gradual process than acute reocclusion: 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty. While the exact mechanism for restenosis is still under active investigation, the general aspects of the restenosis process have been identified.

In the normal arterial will, smooth muscle cells (SMC) proliferate at a low rate (<0.1%/day; ref). SMC in vessel wall exists in a 'contractile' phenotype characterized by 80–90% of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, golgi bodies, and free ribosomes are few and located in the perinuclear region. Extracellular matrix surrounds SMC and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining SMC in the contractile phenotypic state.

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the arterial wall become injured. Cell derived growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), etc. released from platelets (i.e., PDGF) adhering to the damaged arterial luminal surface, invading macrophages and/or leukocytes, or directly from SMC (i.e., BFGF) provoke a proliferation and migratory response in medial SMC.

These cells undergo a phenotypic change from the contractile phenotyope to a 'synthetic' phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum, golgi and free ribosomes. Proliferation/migration usually begins within 1–2 days post-injury and peaks at 2 days in the media, rapidly declining thereafter (Campbell et al., In: *Vascular Smooth Muscle Cells in Culture,* Campbell, J. H. and Campbell, G. R., Eds, CRC Press, Boca Ration, 1987, pp. 39–55); Clowes, A. W. and Schwartz, S. M., Circ. Res. 56:139–145, 1985).

Finally, daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate. Proliferation and migration continues until the damaged luminal endothelial layer regenerates at which time proliferation ceases within the intima, usually within 7–14 days postinjury. The remaining increase in intimal thickening which occurs over the next 3–6 months is due to an increase in extracellular matrix rather than cell number. Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response. (Liu et al., Circulation, 79:1374–1387, 1989).

Patients with symptomatic reocclusion require either repeat PTCA or CABG. Because 30–50% of patients undergoing PTCA will experience restenosis, restenosis has clearly limited the success of PTCA as a therapeutic approach to coronary artery disease. Because SMC proliferation and migration are intimately involved with the pathophysiological response to arterial injury, prevention of SMC proliferation and migration represents a target for pharmacological intervention in the prevention of restenosis.

SUMMARY OF THE INVENTION

Novel Features and Applications to Stent Technology

Currently, attempts to improve the clinical performance of stents have involved some variation of either applying a coating to the metal, attaching a covering or membrane, or embedding material on the surface via ion bombardment. A stent designed to include reservoirs is a new approach which offers several important advantages over existing technologies.

Local Drua Delivery from a Stent to Inhibit Restenosis

In this application, it is desired to deliver a therapeutic agent to the site of arterial injury. The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent. The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks, and be as thin as possible so as to minimize the increase in profile. In addition, the coating material should not contribute to any adverse response by the body (i.e., should be non-thrombogenic, non-inflammatory, etc.). To date, the ideal coating material has not been developed for this application.

An alternative would be to design the stent to contain reservoirs which could be loaded with the drug. A coating or membrane of biocompatable material could be applied over the reservoirs which would control the diffusion of the drug from the reservoirs to the artery wall.

One advantage of this system is that the properties of the coating can be optimized for achieving superior biocompatibility and adhesion properties, without the addition requirement of being able to load and release the drug. The size, shape, position, and number of reservoirs can be used to control the amount of drug, and therefore the dose delivered.

DESCRIPTION OF THE DRAWINGS

The invention will be better understood in connection with the following figures in which FIGS. **1** and **1A** are top views and section views of a stent containing reservoirs as described in the present invention;

FIGS. **2***a* and **2***b* are similar views of an alternate embodiment of the stent with open ends;

FIGS. **3***a* and **3***b* are further alternate figures of a device containing a grooved reservoir; and

FIG. **4** is a layout view of a device containing a reservoir as in FIG. **3**.

DETAILED DESCRIPTION OF THE INVENTION

Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents. Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty. The calcium antagonists have also been unsuccessful in preventing restenosis, although they are still under study. Other agents currently under study include thromboxane inhibitors, prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al., 42 Ann. Rev. Med., 127–132 (1991); Popma et al., 84 *Circulation,* 1426–1436 (1991)).

Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements, thromboxane receptor antagonists, cholesterol lowering agents, and serotonin antagonists has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Franklin, S. M. and Faxon, D. P., 4 Coronary Artery Disease, 232–242 (1993); Serruys, P. W. et al., 88 *Circulation,* (part 1) 1588–1601, (1993).

Conversely, stents have proven useful in preventing reducing the proliferation of restenosis. Stents, such as the stent **10** seen in layout in FIG. **4**, balloon-expandable slotted metal tubes (usually but not limited to stainless steel), which when expanded within the lumen of an angioplastied coronary artery, provide structural support to the arterial wall. This support is helpful in maintaining an open path for blood flow. In two randomized clinical trials, stents were shown to increase angiographic success after PTCA, increase the stenosed blood vessel lumen and to reduce the lesion recurrence at 6 months (Serruys et al., 331 New Eng Jour. Med, 495, (1994); Fischman et al., 331 New Eng Jour. Med, 496–501 (1994). Additionally, in a preliminary trial, heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Additionally, heparin coating appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 93 Circulation, 412–422, (1996). Thus, 1) sustained

mechanical expansion of a stenosed coronary artery has been shown to provide some measure of restenosis prevention, and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs to local, injured tissue off the surface of the stent.

Numerous agents are being actively studied as antiproliferative agents for use in restenosis and have shown some activity in experimental animal models. These include: heparin and heparin fragments (Clowes and Karnovsky, 265 *Nature,* 25–626, (1977); Guyton, J. R. et al. 46 Circ. Res., 625–634, (1980); Clowes, A. W. and Clowes, M. M., 52 Lab. Invest., 611–616, (1985); Clowes, A. W. and Clowes, M. M., 58 Circ. Res., 839–845 (1986);. Majesky et al., 61 Circ Res., 296–300, (1987); Snow et al., 137 Am. J. Pathol., 313–330 (1990); Okada, T. et al., 25 *Neurosurgery,* 92–898, (1989) colchicine (Currier, J. W. et al., 80 *Circulation,* 11–66, (1989), taxol (ref), agiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., 245 Science, 186–188 (1989), angiopeptin (Lundergan, C. F. et al., 17 Am. J. Cardiol. (Suppi. B); 132B–136B (1991), Cyclosporin A (Jonasson, L. et. al., 85 Proc. Natl. Acad. Sci., 2303 (1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., 253 *Science,* 1129–1132 (1991), terbinafine (Nemecek, G. M. et al., 248 J. Pharmacol. Exp. Thera., 1167–11747 (1989), trapidil (Liu, M. W. et al., 81 *Circulation,* 1089–1093 (1990), interferon-gamma (Hansson, G. K. and Holm, 84 *J. Circulation,* 1266–1272 (1991), steroids (Colburn, M. D. et al., 15 J. Vasc. Surg., 510–518 (1992), see also Berk, B. C. et al., 17 J. Am. Coll. Cardiol., 111B–117B (1991), ionizing radiation (ref), fusion toxins (ref) antisense oligonucleotides (ref), gene vectors (ref), and rapamycin (see below).

Of particular interest in rapamycin. Rapamycin is a macrolide antibiotic which blocks IL-2-mediated T-cell proliferation and possesses antiinflammatory activity. While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G_1 to S phase progression of T-cells through the cell cycle by inhibiting specific cell cyclins and cyclin-dependent protein kinases (Siekierka, Immunol. Res. 13: 110–116, 1994). The antiproliferative action of rapamycin is not limited to T-cells; Marx et al. (Circ Res 76:412–417, 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC in vitro while Poon et al. have shown the rat, porcine, and human SMC migratin can also be inhibited by rapamycin (J Clin Invest 98: 2277–2283, 1996). Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response. In fact, the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in a rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al., Transplantation 55:1409–1418, 1993; Gallo et al., in press, (1997)). These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis.

Although the ideal agent for restenosis has not yet been identified, some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury, including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications. Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of SMC combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

Experiments

Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression.

Delivery Methods:

These can vary:

Local delivery of such agents (rapamycin) from the struts of a stent, from a stent graft, grafts, stent cover or sheath.

Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft.

or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein.

or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e.g. vapour deposition methods such as rf-plasma polymerization) and combinations thereof.

Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake

Extravascular delivery by the pericardial route

Extravascular delivery by the advential application of sustained release formulations.

Uses: for inhibition of cell proliferation to prevent neointimal proliferation and restenosis.

prevention of tumor expansion from stents

prevent ingrowth of tissue into catheters and shunts inducing their failure.

1. Experimental Stent Delivery Method—Delivery from Polymer Matrix:

Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0.001 weight % to 30 weight % of drug. Polymers are biocompatible (i.e., not elicit any negative tissue reaction or promote mural thrombus formation) and degradable, such as lactone-based polyesters or copolyesters, e.g., polylactide, polycaprolactonglycolide, polyorthoesters, polyanhydrides; poly-amino acids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, e.g., PEO-PLLA, or blends thereof. Nonabsorbable biocompatible polymers are also suitable candidates. Polymers such as polydimethylsiolxane; poly(ethylene-vingylacetate); acrylate based polymers or copolymers, e.g., poly(hydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters.

Polymer/drug mixture is applied to the surfaces of the stent by either dip-coating, or spray coating, or brush coating or dip/spin coating or combinations thereof, and the solvent allowed to evaporate to leave a film with entrapped rapamycin.

2. Experimental Stent Delivery Method—Delivery from Microporous Depots in Stent Through a Polymer Membrane Coating:

Stent, whose body has been modified to contain micropores or channels is dipped into a solution of Rapamycin, range 0.001 wt % to saturated, in organic solvent such as acetone or methylene chloride, for sufficient time to allow solution to permeate into the pores. (The dipping solution can also be compressed to improve the loading efficiency.) After solvent has been allowed to evaporate, the stent is dipped briefly in fresh solvent to remove excess surface bound drug. A solution of polymer, chosen from any identified in the first experimental method, is applied to the stent as detailed above. This outer layer of polymer will act as diffusion-controller for release of drug.

3. Experimental Stent Delivery Method—Delivery via Lysis of a Covalent Drug Tether

Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization. Covalent bonds such as ester, amides or anhydrides may be suitable for this.

4. Experimental Method—Pericardial Delivery

A: Polymeric Sheet Rapamycin is combined at concentration range previously highlighted, with a degradable polymer such as poly(caprolactone-gylcolide) or non-degradable polymer, e.g., polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10μ to 1000μ. The resulting sheet can be wrapped perivascularly on the target vessel. Preference would be for the absorbable polymer.

B: Conformal Coating: Rapamycin is combined with a polymer that has a melting temperature just above 37° C., range 40°–45° C. Mixture is applied in a molten state to the external side of the target vessel. Upon cooling to body temperature the mixture solidifies conformably to the vessel wall. Both non-degradable and absorbable biocompatible polymers are suitable.

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin. As seen in FIGS. **1***a*, **2***a* and **3***a*, any stent strut **10**, **20**, **30** can be modified to have a certain reservoir or channel **11**, **21**, **31**. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. FIG. **4** shows a stent **40** with a reservoir **45** created at the apex of a flexible strut. Of course, this reservoir **45** is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents.

In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must be kept at a size of about 0.0005" to about 0.003". Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

These and other concepts will are disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be perceived to fall within the scope of the invention which is to be realized from the attached claims and their equivalents.

What is claimed is:

1. A stent having a coating applied thereto, wherein said coating comprises a biocompatible polymer/drug mixture and said drug is rapamycin or a macrocyclic lactone analog thereof.

2. A stent according to claim **1** comprising a generally thin walled cylinder containing a plurality of generally solid struts to which said coating is applied.

3. A stent according to claim **2** further comprising a channel formed in at least one of said struts.

4. A stent according to claim **3**, wherein said channel has a closed perimeter on all sides, an open top and a generally rectangular perimeter, and said channel is smaller in all dimensions than said strut.

5. A stent according to claim **1** wherein the coating is dip-coated onto the stent.

6. A stent according to claim **1** wherein the coating is spray-coated onto the stent.

7. A stent according to claim **1** wherein said rapamycin or macrocyclic lactone analog thereof is contained in the coating at a weight percentage of about 30%.

8. A stent according to claim **1** wherein the coating comprises a degradable polymer.

9. A stent according to claim **1** wherein the coating comprises a nonabsorbable polymer.

10. A stent according to claim **1** wherein the coating comprises a lactone-based polyester; a lactone-based copolyester; a polyanhydride; a polyaminoacid; a polysaccharide; a polyphosphazene; a poly(ether-ester) copolymer; a polydimethylsiloxane; a poly(ethylene)vinylacetate; a poly (hydroxy)ethylmethylmethacrylate; an acrylate based polymer; an acrylate based copolymer; a polyvinyl pyrrolidone; a cellulose ester; a fluorinated polymer; or a blend thereof.

11. A stent according to claim **10** wherein the coating comprises a lactone-based polyester.

12. A stent according to claim **10** wherein the coating comprises a lactone-based copolyester.

13. A stent according to claim **10** wherein the coating comprises a polyanhydride.

14. A stent according to claim **10** wherein the coating comprises a polyaminoacid.

15. A stent according to claim **10** wherein the coating comprises a polysaccharide.

16. A stent according to claim **10** wherein the coating comprises a polyphosphazene.

17. A stent according to claim **10** wherein the coating comprises a poly(ether-ester) copolymer.

18. A stent according to claim **10** wherein the coating comprises a polydimethylsiloxane.

19. A stent according to claim **10** wherein the coating comprises a poly(ethylene)vinylacetate.

20. A stent according to claim **10** wherein the coating comprises a poly(hydroxy)ethylmethylmethacrylate.

21. A stent according to claim **10** wherein the coating comprises an acrylate based polymer.

22. A stent according to claim **10** wherein the coating comprises an acrylate based copolymer.

23. A stent according to claim **10** wherein the coating comprises a polyvinyl pyrrolidone.

24. A stent according to claim **10** wherein the coating comprises a cellulose ester.

25. A stent according to claim **10** wherein the coating comprises a fluorinated polymer.

26. A stent according to claim **10** wherein the fluorinated polymer is polytetrafluoroethylene.

27. A stent according to any one of claims **1** to **26** wherein said drug is a macrocyclic lactone analog of rapamycin.

28. A stent according to any one of claims **1** to **26** that provides a controlled release of said rapamycin or macrocyclic lactone analog thereof over a period of several weeks.

29. A stent according to claim **28** wherein said drug is a macrocyclic lactone analog of rapamycin.

30. A stent according to any one of claims **1** to **26** that releases said rapamycin or macrocyclic lactone analog thereof over a period of at least 14 days.

31. A stent according to claim **30** wherein said drug is a macrocyclic lactone analog of rapamycin.

32. A stent according to any one of claims **1** to **26** wherein said rapamycin or macrocyclic lactone analog thereof is present in a therapeutically beneficial amount to inhibit neointimal proliferation.

33. A stent according to claim **32** wherein said drug is a macrocyclic lactone analog of rapamycin.

34. A stent according to claim 33 that releases said macrocyclic lactone analog of rapamycin over a period of at least 14 days.

35. A stent according to claim 34 wherein the coating comprises a fluorinated polymer.

36. A stent according to claim 35 wherein the coating further comprises an acrylate based polymer or copolymer.

37. A stent according to claim 33 that provides a controlled release of said rapamycin or macrocyclic lactone analog thereof over a period of several weeks.

38. A stent according to claim 37 wherein the coating comprises a fluorinated polymer.

39. A stent according to claim 38 wherein the coating further comprises an acrylate based polymer or copolymer.

40. A device comprising a metallic stent, a biocompatible polymeric carrier and a drug, wherein said drug is rapamycin or a macrocyclic lactone analog thereof and is present in an amount effective to inhibit neointimal proliferation.

41. A device according to claim 40 wherein said polymeric carrier and drug are mixed together.

42. A device according to claim 40 wherein said polymeric carrier is bound to the drug.

43. A device according to claim 40 wherein the drug is entrapped on the surface of the stent by said polymeric carrier.

44. A device according to claim 40 wherein said stent comprises a generally thin walled cylinder containing a plurality of generally solid struts to which said polymeric carrier and drug are applied.

45. A device according to claim 44 further comprising a channel formed in at least one of said struts.

46. A device according to claim 45, wherein said channel has a closed perimeter on all sides, an open top and a generally rectangular perimeter, and said channel is smaller in all dimensions than said strut.

47. A device according to claim 40 wherein the polymeric carrier and drug are dip-coated onto the stent.

48. A device according to claim 40 wherein the polymeric carrier and drug are spray-coated onto the stent.

49. A device according to claim 40 wherein the weight ratio of drug to polymeric carrier is about 3:7.

50. A device according to claim 40 wherein the polymeric carrier comprises a degradable polymer.

51. A device according to claim 40 wherein the polymeric carrier comprises a nonabsorbable polymer.

52. A device according to claim 40 wherein the polymeric carrier comprises a lactone-based polyester; a lactone-based copolyester; a polyanhydride; a polyaminoacid; a polysaccharide; a polyphosphazene; a poly(ether-ester) copolymer; a polydimethylsiloxane; a poly(ethylene)vinylacetate; a poly (hydroxy)ethylmethylmethacrylate; an acrylate based polymer; an acrylate based copolymer; a polyvinyl pyrrolidone; a cellulose ester; a fluorinated polymer; or a blend thereof.

53. A device according to claim 52 wherein the polymeric carrier comprises a lactone-based polyester.

54. A device according to claim 52 wherein the polymeric carrier comprises a lactone-based copolyester.

55. A device according to claim 52 wherein the polymeric carrier comprises a polyanhydride.

56. A device according to claim 52 wherein the polymeric carrier comprises a polyaminoacid.

57. A device according to claim 52 wherein the polymeric carrier comprises a polysaccharide.

58. A device according to claim 52 wherein the polymeric carrier comprises a polyphosphazene.

59. A device according to claim 52 wherein the polymeric carrier comprises a poly(ether-ester) copolymer.

60. A device according to claim 52 wherein the polymeric carrier comprises a polydimethylsiloxane.

61. A device according to claim 52 wherein the polymeric carrier comprises a poly(ethylene)vinylacetate.

62. A device according to claim 52 wherein the polymeric carrier comprises a poly(hydroxy)ethylmethylmethacrylate.

63. A device according to claim 52 wherein the polymeric carrier comprises an acrylate based polymer.

64. A device according to claim 52 wherein the polymeric carrier comprises an acrylate based copolymer.

65. A device according to claim 52 wherein the polymeric carrier comprises a polyvinyl pyrrolidone.

66. A device according to claim 52 wherein the polymeric carrier comprises a cellulose ester.

67. A device according to claim 52 wherein the polymeric carrier comprises a fluorinated polymer.

68. A device according to claim 67 wherein the fluorinated polymer is polytetrafluoroethylene.

69. A device according to any one of claims 40 to 68 wherein said drug is a macrocyclic lactone analog of rapamycin.

70. A device according to any one of claims 40 to 68 that provides a controlled release of said rapamycin or macrocyclic lactone analog thereof over a period of several weeks.

71. A device according to claim 70 wherein said drug is a macrocyclic lactone analog of rapamycin.

72. A device according to claim 71 wherein the polymeric carrier comprises a fluorinated polymer.

73. A device according to claim 72 wherein the polymeric carrier further comprises an acrylate based polymer or copolymer.

74. A device according to any one of claims 40 to 68 that releases said drug over a period of at least 14 days.

75. A device according to claim 74 wherein said drug is a macrocyclic lactone analog of rapamycin.

76. A device according to claim 75 wherein the polymeric carrier comprises a fluorinated polymer.

77. A device according to claim 76 wherein the polymeric carrier further comprises an acrylate based polymer or copolymer.

* * * * *

Exhibit F

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/466,983	06/12/2007	7229473	CRDS-0066	2883

45511 7590 05/23/2007

WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Robert Falotico, Bell Mead, NJ;
Gerard H. Llanos, Stewartsville, NJ;

U.S. PATENT NO. 7,229,473

Exhibit G

Healthcare
Medical Devices

JNJ: TAKES OFF THE GLOVES IN ITS FIGHT WITH BOSTON SCIENTIFIC FOR GUIDANT

Johnson & Johnson
Larry Biegelsen • 212.778.5825 • lawrence_biegelsen@prusec.com
Steve Beuchaw • 212.778.1515 • steve_beuchaw@prusec.com

JNJ ($61.10, NYSE)	
Current:	Underweight
Risk:	Low
Target:	$59.00
Industry:	Favorable

All important disclosures and Regulation AC disclosure can be found at the end of this report, starting at page 6, under the section entitled Important Disclosures and Regulation AC Disclosure, respectively.

Includes Option Expenses

	FY	REV	EPS	P/E	1Q	2Q	3Q	4Q
Actual	12/04	$47,348.0E	$2.99E	20.6X	$0.80A	$0.79A	$0.75A	$0.64A
Current	12/05	$51,214.0E	$3.37E	18.2X	$0.94A	$0.90A	$0.85A	$0.69E
Current	12/06	$53,758.0E	$3.61E	17.0X	$1.01E	$0.95E	$0.89E	$0.76E

Without Option Expenses

	FY	REV	EPS	P/E	1Q	2Q	3Q	4Q
Actual	12/04	$47,348.0E	$3.10A	19.8X	$0.83A	$0.82A	$0.78A	$0.67A
Current	12/05	$51,214.0E	$3.49E	17.6X	$0.97A	$0.93A	$0.87A	$0.72E
Current	12/06	$53,758.0E	$3.74E	16.4X	$1.04E	$0.98E	$0.93E	$0.79E

Avg. Volume: **8,700,000**
Market Cap: **$191,808 m**
Shares: **3,119.84 m**

Div/Yield: **1.32/2.15%**
52w Range: **70.00-59.80**

EPS Growth: **NA**
P/E / Growth: **NM**

HIGHLIGHTS

- As the 1/25 deadline to make a counter-offer for GDT approaches, JNJ is communicating to the Street that BSX's $80/share offer for GDT is fraught with uncertainty which leads us to believe that JNJ is still very interested in acquiring GDT and that JNJ will likely increase its offer at least one more time.
- We believe JNJ will have to raise its offer to about $78/share from $71/share in order to gain the GDT board's approval.
- Although a JNJ offer of $78/share would be 3% below BSX's, there is precedent for a board to accept a lower offer. In 5/05, Verizon acquired MCI for $8.44B or 13% less than what Qwest offered because Verizon was seen as a more stable company.
- JNJ claims that 2 of its patents may be infringed if a company tries to launch a drug-eluting stent coated with a rapamycin derivative such as ABT's zotarolimus and GDT's everolimus. The potential for JNJ to prevent ABT and BSX from marketing the Xience-V DES, could give the GDT board pause for approving a BSX-GDT merger.
- Our analysis indicates that an offer of $78/share for GDT would be slightly more dilutive for JNJ compared to its current $71/share offer but still accretive on a cash basis in '08. In addition, our analysis indicates that JNJ could offer $90/share for GDT before an acquisition of STJ is more attractive.

DISCUSSION

As the January 25th deadline for JNJ to make a counter-offer for Guidant (GDT-$75.89; Neutral Weight Rated) approaches, JNJ is communicating to the Street that Boston Scientific's (BSX-$23.36; Neutral Weight Rated) $80/share offer for GDT is fraught with uncertainty. This leads us to believe that JNJ is still very much interested in acquiring GDT and that JNJ will likely increase its offer for GDT at least one more time. We believe JNJ will have to increase its offer to at least $78/share from its previous offer of $71/share if it hopes to gain the GDT board's approval. Although a JNJ offer of $78/share would be 3% below BSX's, there is precedent for a board and shareholders to accept a lower offer. In May 2005, Verizon acquired MCI for $8.44 billion or 13% less than what Qwest offered because VZ was seen as a more stable company. During the bidding process, Q forced VZ to raise its offer for MCI from $20.35/share to $26/share. Although the situation with VZ and Q is not a perfect analogy, we could envision a similar scenario playing out with GDT given the lower risk associated with the JNJ offer and the greater liquidity of JNJ shares compared to BSX shares once a deal is completed. Interestingly, BSX's stock price is moving closer to the lower end of the collar ($22.62). If BSX's stock price falls to $22.00, its offer for GDT would become $79/share (see Figure 1 below).

Figure 1: Impact of Collar on BSX's Offer For GDT if BSX's Share Price Reaches $22.00

BSX Current Price:	$23.36
Collar Max:	$28.86
Collar Min:	$22.62
Proposed Cash Component of BSX Offer:	$42.00
Proposed Stock Component of BSX Offer:	$38.00
Proposed Total BSX Offer for GDT:	$80.00
Assumed BSX Stock Price:	**$22.00**
Collared Exchange Ratio:	1.68
Resulting Stock Component of BSX Offer:	$36.96
Resulting Total Value of BSX Offer:	$78.96
Lost Value Per GDT Share:	**-$1.04**
GDT Fully Diluted Shares (mm):	335
Market Value Impact ($mm):	-$349

Source: Company reports, Prudential Equity Group, LLC estimates, Reuters.

JNJ's acquisition of GDT has already received regulatory clearance in the U.S. and E.U. In order to receive approval from the FTC, JNJ was forced to license out rapid exchange (RX) stent technology as well as certain JNJ patents which cover the use of rapamycin derivatives such as Novartis's (NVS: $54.98; Overweight rated by Prudential Equity Group's Senior Pharmaceutical Analyst, Tim Anderson) everolimus and Abbott Labs' (ABT-$40.60; Neutral Weight Rated) zotarolimus on a stent because the FTC wanted to ensure that ABT would be a viable competitor in the drug-eluting stent (DES) market. ABT is currently developing a DES using its proprietary drug, zotarolimus which is also used on Medtronic's (MDT-$58.99; Overweight Rated) Endeavor DES. The clinical results for Endeavor have

been mixed thus far and data with ABT's DES, ZoMaxx, have not been presented yet so it's unclear how competitive ZoMaxx will be. Under the JNJ-GDT deal, ABT would be able to potentially develop a second DES using everolimus. Although ABT does not currently have the rights to use the drug everolimus on a stent from NVS, the drug's originator, it is our understanding that acquiring the rights would not be a major obstacle if ABT wanted to develop an everolimus-coated stent.

If BSX acquires GDT, BSX would sell GDT's vascular intervention (VI) business, including shared rights to GDT's promising everolimus-coated stent, Xience-V, to ABT. Although JNJ's patents have never been litigated, JNJ believes it has a strong intellectual property (IP) position with regard to the use of rapamycin derivatives on a stent. JNJ could pursue a preliminary injunction if ABT and BSX try to launch an everolimus-coated or zotarolimus-coated stent. The potential for JNJ to prevent ABT and BSX from marketing the Xience-V DES, could give the GDT board and the FTC pause for approving a BSX-GDT merger. According to JNJ, the key patents are the Falotico (6,776,796) and Wright (6,5857,64) patents.

Our analysis indicates that an offer of $78/share for GDT would be slightly more dilutive for JNJ on a cash and GAAP basis compared to its current $71/share offer but still accretive on a cash basis in 2008 (see merger models at the end of this note). In our model, we assume that JNJ raises the cash portion of its offer by $6/share. In addition, our analysis indicates that JNJ could offer $90/share for GDT before an acquisition of St. Jude is more attractive financially for JNJ (also shown at the end of this note).

VALUATION AND RISKS

Our price target of $59 is the average of our price targets for J&J with and without GDT. For JNJ alone, we apply a target multiple of 13.0x our 2008 EPS of $4.38 to arrive at a target price of $57. We use a multiple of 13x, a 7% discount to the average multiple of the large cap U.S. pharmaceutical group, which is appropriate in our view because of JNJ's slowing pharmaceutical growth (the source of 50% of JNJ's profits). We use 2008 EPS because that is the first year in which the GDT acquisition is expected to be accretive. For JNJ with GDT, we apply a target multiple of 14x our combined JNJ-GDT EPS estimate of $4.40 to arrive at a target price of $62. We use a multiple of 14x because this represents a 15% discount to our coverage universe which we believe is appropriate given the combined entity's below average growth prospects. Again, we use 2008 EPS because that is the first year in which the GDT acquisition would be accretive.

The average of the two scenarios yields a target price of $59.

Key risks to the achievement of our price target are: 1) less price erosion in the U.S. EPO market than we model; 2) branded and generic competition in the European EPO market takes less share of the market than we model; 3) Cypher captures greater market share from Taxus than what we model; 4) key pharmaceutical pipeline products such as paliperidone ER exceed our expectations; 6) JNJ acquires GDT; 7) JNJ's operating expenses grow more slowly than what we model; and 8) JNJ acquires additional late stage pharmaceutical products.

BUSINESS

Johnson & Johnson (JNJ), is the world's most comprehensive and broadly based manufacturer of health care products, as well as a provider of related services, for the consumer, pharmaceutical, and medical devices and diagnostics markets.

January 20, 2006

Healthcare
Medical Devices

CHARTS/MODELS

Guidant Impact on JNJ Cash EPS, GAAP EPS and Growth - $71per Share (57% cash/43% stock)

In Millions, Except Per Share Data

Revenue Impact of GDT ($MM)	2005 E	2006 E	2007 E	2008 E	2009 E	2010 E	CAGR '05-'08	CAGR '05-'10	CAGR '07-'10
JNJ Sales (ex-GDT)	$51,185	$53,819	$57,263	$60,998	$63,778	$68,781	6.0%	6.1%	6.3%
Total Incremental Sales (Guidant)	$3,549	$3,899	$4,479	$5,235	$5,942	$6,500	13.8%	12.9%	13.2%
Total JNJ-GDT Pro Forma Sales	$54,735	$57,718	$61,742	$66,231	$69,720	$75,280	6.6%	6.6%	6.8%
Pro-Forma Y-Y %		*5.5%*	*7.0%*	*7.3%*	*5.3%*	*8.0%*			
JNJ Growth Ex-GDT	*6.1%*	*5.1%*	*6.4%*	*6.5%*	*4.6%*	*7.9%*			
Sales Growth Impact of GDT		*0.3%*	*0.6%*	*0.8%*	*0.7%*	*0.1%*			
Profit Impact									
Total Incremental Operating Profit		832	1,254	1,591	1,860	2,132			
Merger Synergies		0	0	0	0	0			
GDT Other Expenses		12	23	41	53	53			
Profit w/Synergies and GDT Other Expenses		820	1,231	1,551	1,807	2,079			
After Tax GDT Income		623	936	1,178	1,373	1,580			
Impact on JNJ Interest Income - After Tax		-378	-358	-329	-293	-249			
Net Impact on JNJ Net Profit		245	577	850	1,081	1,331			

	2005 E	2006 E	2007 E	2008 E	2009 E	2010 E	CAGR '05-'08	CAGR '05-'10	CAGR '07-'10
Pre GDT JNJ EPS	3.49	3.74	4.09	4.38	4.52	4.98	7.9%	7.4%	6.8%
JNJ Cash EPS with GDT		3.62	4.06	4.42	4.63	5.15	8.2%	8.1%	8.2%
GDT Impact on Cash EPS		-0.11	-0.02	0.05	0.11	0.17			
Amort of Intang. Per Share (Non-Cash)		(0.18)	(0.16)	(0.18)	(0.16)	(0.16)			
JNJ GAAP EPS with GDT		$3.46	$3.90	$4.28	$4.47	$4.99			
GDT Impact on JNJ GAAP EPS		(0.27)	(0.19)	(0.12)	(0.05)	0.00			
Growth Impact of GDT									
Pre GDT JNJ EPS Y-Y		7.1%	9.4%	7.1%	3.3%	10.2%			
JNJ EPS ex-Amort of GDT Intangibles		3.9%	12.1%	8.9%	4.7%	11.1%			
Impact of GDT ex-Amort. of Intangibles		-3.2%	2.7%	1.8%	1.4%	1.0%			
JNJ GAAP EPS Y-Y with GDT Intangibles		-0.8%	12.8%	9.3%	4.9%	11.5%			
GDT Impact on GAAP EPS Growth		-7.9%	3.3%	2.2%	1.6%	1.4%			

A Actuals
E Prudential Equity Group Estimates
Source: Prudential Equity Group, LLC, and Company Reports
Assumes JNJ shares are worth $62.00

January 20, 2006

Healthcare
Medical Devices

Guidant Impact on JNJ Cash EPS, GAAP EPS and Growth - $78 per Share (61% cash/39% stock)

In Millions, Except Per Share Data

Revenue Impact of GDT ($MM)	2005 E	2006 E	2007 E	2008 E	2009 E	2010 E	CAGR '05-'08	CAGR '05-'10	CAGR '07-'10
JNJ Sales (ex-GDT)	$51,185	$53,819	$57,263	$60,998	$63,778	$68,781	6.0%	6.1%	6.3%
Total Incremental Sales (Guidant)	$3,549	$3,899	$4,479	$5,235	$5,942	$6,500	13.8%	12.9%	13.2%
Total JNJ-GDT Pro Forma Sales	$54,735	$57,718	$61,742	$66,231	$69,720	$75,290	6.6%	6.6%	6.8%
Pro-Forma Y-Y %		*5.5%*	*7.0%*	*7.3%*	*5.3%*	*8.0%*			
JNJ Growth Ex-GDT	*8.1%*	*5.1%*	*6.4%*	*6.5%*	*4.6%*	*7.9%*			
Sales Growth Impact of GDT		*0.3%*	*0.6%*	*0.8%*	*0.7%*	*0.1%*			
Profit Impact									
Total Incremental Operating Profit		832	1,254	1,591	1,880	2,132			
Merger Synergies		0	0	0	0	0			
GDT Other Expenses		12	23	41	53	53			
Profit w/Synergies and GDT Other Expenses		820	1,231	1,551	1,807	2,079			
After Tax GDT Income		623	936	1,178	1,373	1,580			
Impact on JNJ Interest Income - After Tax		-458	-439	-409	-373	-329			
Net Impact on JNJ Net Profit		165	497	769	1,000	1,251			

	2005 E	2006 E	2007 E	2008 E	2009 E	2010 E	CAGR '05-'08	CAGR '05-'10	CAGR '07-'10
Pre GDT JNJ EPS	3.48	3.74	4.09	4.38	4.52	4.98	7.9%	7.4%	6.8%
JNJ Cash EPS with GDT		3.80	4.04	4.40	4.81	5.12	8.0%	8.0%	8.3%
GDT Impact on Cash EPS		-0.14	-0.05	0.02	0.09	0.14			
Amort of Intang. Per Share (Non-Cash)		(0.16)	(0.16)	(0.16)	(0.16)	(0.16)			
JNJ GAAP EPS with GDT		$3.44	$3.87	$4.23	$4.44	$4.96			
GDT Impact on JNJ GAAP EPS		(0.30)	(0.21)	(0.14)	(0.08)	(0.02)			
Growth Impact of GDT									
Pre GDT JNJ EPS Y-Y		7.1%	9.4%	7.1%	3.3%	10.2%			
JNJ EPS ex-Amort of GDT Intangibles		3.2%	12.2%	9.0%	4.8%	11.2%			
Impact of GDT ex-Amort. of Intangibles		-3.9%	2.8%	1.8%	1.5%	1.0%			
JNJ GAAP EPS Y-Y with GDT Intangibles		-1.5%	12.7%	9.3%	4.8%	11.6%			
GDT Impact on GAAP EPS Growth		-8.8%	3.3%	2.2%	1.7%	1.4%			

A Actuals
E Prudential Equity Group Estimates
Source: Prudential Equity Group, LLC, and Company Reports
Assumes JNJ shares are worth $62.00

To view charts associated with those stocks mentioned in this report, please visit http://cm1.prusec.com.

REGULATION AC DISCLOSURE

Larry Biegelsen is principally responsible for the analysis of any security or issuer included in this report and certifies that the views expressed accurately reflect such research analyst's personal views about subject securities or issuers and certifies that no part of his or her compensation was, is, or will be directly or indirectly related to the specific recommendation or views contained in the research report.

IMPORTANT DISCLOSURES

Prudential Financial or its affiliates beneficially owns 1% or more of any class of common equity securities of St. Jude Medical.

When we assign an **Overweight** rating, we mean that we expect that the stock's total return will exceed the average total return of all of the stocks covered by the analyst (or analyst team). Our investment time frame is 12-18 months except as otherwise specified by the analyst in the report.

When we assign a **Neutral** Weight rating, we mean that we expect that the stock's total return will be in line with the average total return of all of the stocks covered by the analyst (or analyst team). Our investment time frame is 12-18 months except as otherwise specified by the analyst in the report.

When we assign an **Underweight** rating, we mean that we expect that the stock's total return will be below the average total return of all of the stocks covered by the analyst (or analyst team). Our investment time frame is 12-18 months except as otherwise specified by the analyst in the report.

ANALYST UNIVERSE COVERAGE:
Larry Biegelsen: Abbott Laboratories, Boston Scientific, Edwards Lifesciences, Johnson & Johnson, St. Jude Medical, Medtronic, Inc., Guidant Corp.
Tim Anderson, M.D.: Schering-Plough, Eli Lilly, Forest Laboratories, Merck & Co., Bristol-Myers Squibb, Wyeth, Pfizer, Inc., GlaxoSmithKline plc, AstraZeneca, Novartis AG, Roche Holding AG, Sanofi-Aventis Group.

Rating Distribution

01/19/06	Firm	Firm's Investment Banking Clients	Sector	Sector's Investment Banking Clients
Overweight(Buy)*	30%	0%	29%	0%
Neutral Weight(Hold)*	48%	0%	53%	0%
Underweight(Sell)*	22%	0%	17%	0%

Excludes Closed End Funds

12/30/05	Firm	Firm's Investment Banking Clients	Sector	Sector's Investment Banking Clients
Overweight(Buy)*	30%	0%	31%	0%
Neutral Weight(Hold)*	47%	0%	52%	0%
Underweight(Sell)*	23%	0%	17%	0%

Excludes Closed End Funds

09/30/05		Firm's		Sector's

Healthcare
Medical Devices

	Firm	Investment Banking Clients	Sector	Investment Banking Clients
Overweight(Buy)*	32%	0%	29%	0%
Neutral Weight(Hold)*	44%	0%	49%	0%
Underweight(Sell)*	24%	0%	22%	0%

Excludes Closed End Funds

06/30/05	Firm	Firm's Investment Banking Clients	Sector	Sector's Investment Banking Clients
Overweight(Buy)*	32%	0%	31%	0%
Neutral Weight(Hold)*	45%	0%	51%	0%
Underweight(Sell)*	22%	0%	19%	0%

Excludes Closed End Funds

* In accordance with applicable rules and regulations, we note above parenthetically that our stock ratings of "Overweight," "Neutral Weight," and "Underweight" most closely correspond with the more traditional ratings of "Buy," "Hold," and "Sell," respectively; however, please note that their meanings are not the same. (See the definitions above.) We believe that an investor's decision to buy or sell a security should always take into account, among other things, that the investor's particular investment objectives and experience, risk tolerance, and financial circumstances. Rather than being based on an expected deviation from a given benchmark (as buy, hold and sell recommendations often are), our stock ratings are determined on a relative basis (see the foregoing definitions).

Prior to September 8, 2003 our rating definitions were Buy, Hold, Sell. They are defined as follows:

When we assign a **Buy** rating, we mean that we believe that a stock of average or below-average risk offers the potential for total return of 15% or more over the next 12 to 18 months. For higher-risk stocks, we may require a higher potential return to assign a Buy rating. When we reiterate a Buy rating, we are stating our belief that our price target is achievable over the next 12 to 18 months.

When we assign a **Sell** rating, we mean that we believe that a stock of average or above-average risk has the potential to decline 15% or more over the next 12 to 18 months. For lower-risk stocks, a lower potential decline may be sufficient to warrant a Sell rating. When we reiterate a Sell rating, we are stating our belief that our price target is achievable over the next 12 to 18 months.

A **Hold** rating signifies our belief that a stock does not present sufficient upside or downside potential to warrant a Buy or Sell rating, either because we view the stock as fairly valued or because we believe that there is too much uncertainty with regard to key variables for us to rate the stock a Buy or Sell.

When we assign an industry rating of Favorable, we mean that generally industry fundamentals/stock prospects are improving.

When we assign an industry rating of Neutral, we mean that generally industry fundamentals/stock prospects are stable.

When we assign an industry rating of Unfavorable, we mean that generally industry fundamentals/stock prospects are deteriorating.

Healthcare
Medical Devices

Ratings History: JNJ

Rating Changes			
Date	From	To	Analyst
12/08/05	--	UNDR	Biegelsen
03/31/05	OVER	--	Faulkner
08/20/04	--	OVER	Faulkner

Target Price Changes			
Date	From	To	Analyst
12/08/05	--	59.00	Biegelsen
03/31/05	74.00	--	Faulkner
12/16/04	61.00	74.00	Faulkner
08/20/04	--	61.00	Faulkner

Additional Information

Price Target – Methods/Risks

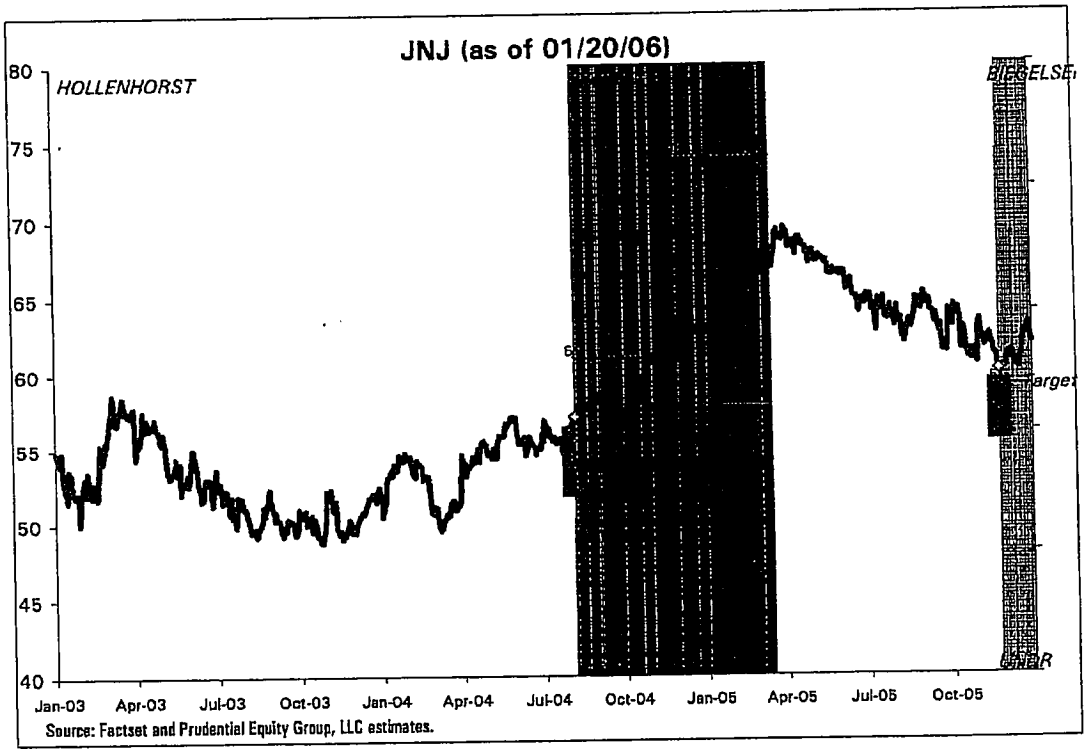
The methods used to determine the price target generally are based on future earning estimates, product performance expectations, cash flow methodology, historical and/or relative valuation multiples. The risks associated with achieving the price target generally include customer spending, industry competition and overall market conditions.

Additional risk factors as they pertain to the analyst's specific investment thesis can be found within the report.

Price History: JNJ

January 20, 2006

Healthcare
Medical Devices



When recommending the purchase or sale of a security, Prudential Equity Group, LLC is subject to a conflict of interest because should such advice be followed, and result in a transaction being executed through the firm, Prudential Equity Group, LLC may earn brokerage compensation on the transaction. In addition, any order placed with Prudential Equity Group, LLC may be executed on either an agency basis resulting in a commission payment to Prudential Equity Group, LLC or on a principal basis, versus Prudential Equity Group, LLC's proprietary account, resulting in a mark-up or mark-down by Prudential Equity Group, LLC.

Any OTC-traded securities or non-U.S. companies mentioned in this report may not be cleared for sale in all jurisdictions.
Securities products and services are offered through Prudential Equity Group, LLC, a Prudential Financial company.

Information contained herein is based on data obtained from recognized statistical services, issuer reports or communications, or other sources, believed to be reliable. Any statements nonfactual in nature constitute only current opinions, which are subject to change.

There are risks inherent in international investments, which may make such investments unsuitable for certain clients. These include, for example, economic, political, currency exchange rate fluctuations, and limited availability of information on international securities. Prudential Equity Group LLC, and its affiliates, make no representation that the companies which issue securities that are the subject of their research reports are in compliance with certain informational reporting requirements imposed by the Securities Exchange Act of 1934. Sales of securities covered by this report may be made only in those jurisdictions where the security is qualified for sale. The contents of this publication have been approved for distribution by Bache Financial Limited, which is authorised and regulated by The Financial Services Authority. We recommend that you obtain the advice of your Registered Representative regarding this or other investments.

If you did not receive this research report directly from Prudential Equity Group, LLC ("PEG") or Bache Financial Ltd ("BFL"), your access to, and receipt of, this report does not by itself operate to establish a client-broker relationship between you and PEG or BFL, as the case may be. Accordingly, please direct any questions you may have regarding this report to the registered representative employed by the securities firm at which your account is held who is assigned to service your account, and not to PEG or any PEG analyst whose name appears above. Please note that PEG or BFL, as the case may be, bears no responsibility for any recommendation(s) or advice that such securities firm or its registered representatives may provide to you, regardless of whether any such recommendation or advice is based in whole or in part on this report.

Additional information on the securities discussed herein is available upon request. The applicable disclosures can be obtained by writing to: Prudential Equity Group, LLC, 1 New York Plaza – 17th floor, New York, New York, 10292 Attn: Equity Research.

Prudential Equity Group, LLC and Prudential Financial, Inc. of the United States are not affiliated with Prudential plc of the United Kingdom.

Guidant Impact on JNJ Cash EPS, GAAP EPS and Growth - $71per Share (57% ca

In Millions, Except Per Share Data

							CAGR		
Revenue Impact of GDT ($	**2005 E**	**2006 E**	**2007 E**	**2008 E**	**2009 E**	**2010 E**	**'05-'08**	**'05-'10**	**'07-'10**
JNJ Sales (ex-GDT)	$51,185	$53,819	$57,263	$60,996	$63,778	$68,791	6.0%	6.1%	6.3%
Total Incremental Sales (Gui	$3,549	$3,899	$4,479	$5,235	$5,942	$6,500	13.8%	12.9%	13.2%
Total JNJ-GDT Pro Forma S	**$54,735**	**$57,718**	**$61,742**	**$66,231**	**$69,720**	**$75,290**	6.6%	6.6%	6.8%
Pro-Forma Y-Y %		*5.5%*	*7.0%*	*7.3%*	*5.3%*	*8.0%*			
JNJ Growth Ex-GDT	*8.1%*	*5.1%*	*6.4%*	*6.5%*	*4.6%*	*7.9%*			
Sales Growth Impact of GDT		*0.3%*	*0.6%*	*0.8%*	*0.7%*	*0.1%*			
Profit Impact									
Total Incremental Operating Profit		832	1,254	1,591	1,860	2,132			
Merger Synergies		0	0	0	0	0			
GDT Other Expenses		12	23	41	53	53			
Profit w/Synergies and GDT Other Expe		820	1,231	1,551	1,807	2,079			
After Tax GDT Income		623	936	1,178	1,373	1,580			
Impact on JNJ Interest Income - After T		-378	-358	-329	-293	-249			
Net Impact on JNJ Net Profit		**245**	**577**	**850**	**1,081**	**1,331**			
							CAGR		
	2005 E	**2006 E**	**2007 E**	**2008 E**	**2009 E**	**2010 E**	**'05-'08**	**'05-'10**	**'07-'10**
Pre GDT JNJ EPS	3.49	3.74	4.09	4.38	4.52	4.98	7.9%	7.4%	6.8%
JNJ Cash EPS with GDT		**3.62**	**4.06**	**4.42**	**4.63**	**5.15**	8.2%	8.1%	8.2%
GDT Impact on Cash EPS		-0.11	-0.02	0.05	0.11	0.17			
Amort of Intang. Per Share (Non-Cash)		(0.16)	(0.16)	(0.16)	(0.16)	(0.16)			
JNJ GAAP EPS with GDT		$3.46	$3.90	$4.26	$4.47	$4.99			
GDT Impact on JNJ GAAP EPS		(0.27)	(0.19)	(0.12)	(0.05)	0.00			
Growth Impact of GDT									
Pre GDT JNJ EPS Y-Y		7.1%	9.4%	7.1%	3.3%	10.2%			
JNJ EPS ex-Amort of GDT Intangibles		3.9%	12.1%	8.9%	4.7%	11.1%			
Impact of GDT ex-Amort. of Intangibles		-3.2%	2.7%	1.8%	1.4%	1.0%			
JNJ GAAP EPS Y-Y with GDT Intangibl		-0.8%	12.6%	9.3%	4.9%	11.5%			
GDT Impact on GAAP EPS Growth		-7.9%	3.3%	2.2%	1.6%	1.4%			

A Actuals
E Prudential Equity Group Estimates
Source: Prudential Equity Group, LLC, and Company Reports
Assumes JNJ shares are worth $62.00

Larry Biegelsen I 212 778 5825 I Lawrence_Biegelsen@prusec.com
Prudential Equity Group, LLC I One New York Plaza, 15th Floor I New York, NY 10292

Guidant Impact on JNJ Cash EPS, GAAP EPS and Growth - $78 per Share (61% ca

In Millions, Except Per Share Data							CAGR		
Revenue Impact of GDT ($	**2005 E**	**2006 E**	**2007 E**	**2008 E**	**2009 E**	**2010 E**	**'05-'08**	**'05-'10**	**'07-'10**
JNJ Sales (ex-GDT)	$51,185	$53,819	$57,263	$60,996	$63,778	$68,791	6.0%	6.1%	6.3%
Total Incremental Sales (Gui	$3,549	$3,899	$4,479	$5,235	$5,942	$6,500	13.8%	12.9%	13.2%
Total JNJ-GDT Pro Forma S	**$54,735**	**$57,718**	**$61,742**	**$66,231**	**$69,720**	**$75,290**	6.6%	6.6%	6.8%
Pro-Forma Y-Y %		*5.5%*	*7.0%*	*7.3%*	*5.3%*	*8.0%*			
JNJ Growth Ex-GDT	*8.1%*	*5.1%*	*6.4%*	*6.5%*	*4.6%*	*7.9%*			
Sales Growth Impact of GDT		*0.3%*	*0.6%*	*0.8%*	*0.7%*	*0.1%*			
Profit Impact									
Total Incremental Operating Profit		832	1,254	1,591	1,860	2,132			
Merger Synergies		0	0	0	0	0			
GDT Other Expenses		12	23	41	53	53			
Profit w/Synergies and GDT Other Expe		820	1,231	1,551	1,807	2,079			
After Tax GDT Income		623	936	1,178	1,373	1,580			
Impact on JNJ Interest Income - After T		-458	-439	-409	-373	-329			
Net Impact on JNJ Net Profit		**165**	**497**	**769**	**1,000**	**1,251**			
							CAGR		
	2005 E	**2006 E**	**2007 E**	**2008 E**	**2009 E**	**2010 E**	**'05-'08**	**'05-'10**	**'07-'10**
Pre GDT JNJ EPS	3.49	3.74	4.09	4.38	4.52	4.98	7.9%	7.4%	6.8%
JNJ Cash EPS with GDT		**3.60**	**4.04**	**4.40**	**4.61**	**5.12**	8.0%	8.0%	8.3%
GDT Impact on Cash EPS		-0.14	-0.05	0.02	0.09	0.14			
Amort of Intang. Per Share (Non-Cash)		(0.16)	(0.16)	(0.16)	(0.16)	(0.16)			
JNJ GAAP EPS with GDT		$3.44	$3.87	$4.23	$4.44	$4.96			
GDT Impact on JNJ GAAP EPS		(0.30)	(0.21)	(0.14)	(0.08)	(0.02)			
Growth Impact of GDT									
Pre GDT JNJ EPS Y-Y		7.1%	9.4%	7.1%	3.3%	10.2%			
JNJ EPS ex-Amort of GDT Intangibles		3.2%	12.2%	9.0%	4.8%	11.2%			
Impact of GDT ex-Amort. of Intangibles		-3.9%	2.8%	1.8%	1.5%	1.0%			
JNJ GAAP EPS Y-Y with GDT Intangibl		-1.5%	12.7%	9.3%	4.9%	11.6%			
GDT Impact on GAAP EPS Growth		-8.6%	3.3%	2.2%	1.7%	1.4%			
A Actuals									
E Prudential Equity Group Estimates									
Source: Prudential Equity Group, LLC, and Company Reports									
Assumes JNJ shares are worth $62.00									

Larry Biegelsen I 212 778 5825 I Lawrence_Biegelsen@prusec.com
Prudential Equity Group, LLC I One New York Plaza, 15th Floor I New York, NY 10292

Guidant Impact on JNJ Cash EPS, GAAP EPS and Growth - $90 per Share (66% ca

In Millions, Except Per Share Data							CAGR		
Revenue Impact of GDT ($	**2005 E**	**2006 E**	**2007 E**	**2008 E**	**2009 E**	**2010 E**	**'05-'08**	**'05-'10**	**'07-'10**
JNJ Sales (ex-GDT)	$51,185	$53,819	$57,263	$60,996	$63,778	$68,791	6.0%	6.1%	6.3%
Total Incremental Sales (Gui	$3,549	$3,899	$4,479	$5,235	$5,942	$6,500	13.8%	12.9%	13.2%
Total JNJ-GDT Pro Forma S	**$54,735**	**$57,718**	**$61,742**	**$66,231**	**$69,720**	**$75,290**	6.6%	6.6%	6.8%
Pro-Forma Y-Y %		*5.5%*	*7.0%*	*7.3%*	*5.3%*	*8.0%*			
JNJ Growth Ex-GDT	*8.1%*	*5.1%*	*6.4%*	*6.5%*	*4.6%*	*7.9%*			
Sales Growth Impact of GDT		*0.3%*	*0.6%*	*0.8%*	*0.7%*	*0.1%*			
Profit Impact									
Total Incremental Operating Profit		832	1,254	1,591	1,860	2,132			
Merger Synergies		0	0	0	0	0			
GDT Other Expenses		12	23	41	53	53			
Profit w/Synergies and GDT Other Expe		820	1,231	1,551	1,807	2,079			
After Tax GDT Income		623	936	1,178	1,373	1,580			
Impact on JNJ Interest Income - After T		-596	-577	-547	-511	-467			
Net Impact on JNJ Net Profit		**27**	**359**	**632**	**862**	**1,113**			
							CAGR		
	2005 E	**2006 E**	**2007 E**	**2008 E**	**2009 E**	**2010 E**	**'05-'08**	**'05-'10**	**'07-'10**
Pre GDT JNJ EPS	3.49	3.74	4.09	4.38	4.52	4.98	7.9%	7.4%	6.8%
JNJ Cash EPS with GDT		**3.56**	**3.99**	**4.35**	**4.56**	**5.08**	7.7%	7.8%	8.4%
GDT Impact on Cash EPS		-0.18	-0.09	-0.02	0.04	0.10			
Amort of Intang. Per Share (Non-Cash)		(0.16)	(0.16)	(0.16)	(0.16)	(0.16)			
JNJ GAAP EPS with GDT		$3.39	$3.83	$4.19	$4.40	$4.92			
GDT Impact on JNJ GAAP EPS		(0.34)	(0.26)	(0.18)	(0.12)	(0.06)			
Growth Impact of GDT									
Pre GDT JNJ EPS Y-Y		7.1%	9.4%	7.1%	3.3%	10.2%			
JNJ EPS ex-Amort of GDT Intangibles		2.0%	12.3%	9.1%	4.8%	11.3%			
Impact of GDT ex-Amort. of Intangibles		-5.2%	2.9%	1.9%	1.5%	1.1%			
JNJ GAAP EPS Y-Y with GDT Intangibl		-2.7%	12.9%	9.4%	5.0%	11.7%			
GDT Impact on GAAP EPS Growth		-9.8%	3.5%	2.3%	1.7%	1.5%			
A Actuals									
E Prudential Equity Group Estimates									
Source: Prudential Equity Group, LLC, and Company Reports									
Assumes JNJ shares are worth $62.00									

Larry Biegelsen I 212 778 5825 I Lawrence_Biegelsen@prusec.com
Prudential Equity Group, LLC I One New York Plaza, 15th Floor I New York, NY 10292

St. Jude Impact on JNJ Cash EPS, GAAP EPS and Growth - $62 Per Share (60% Cas

In Millions, Except Per Share Data

							CAGR		
Revenue Impact of STJ ($MM	**2005 E**	**2006 E**	**2007 E**	**2008 E**	**2009 E**	**2010 E**	**'05-'08**	**'05-'10**	**'07-'10**
JNJ Sales (ex-STJ)	$51,185	$53,819	$57,263	$60,996	$63,778	$68,791	6.0%	6.1%	6.3%
Total Incremental Sales (STJ)	$2,922	$3,543	$3,930	$4,369	$4,883	$5,456	14.3%	13.3%	11.6%
Total JNJ-STJ Pro Forma Sales	**$54,108**	**$57,361**	**$61,193**	**$65,365**	**$68,661**	**$74,247**	6.5%	6.5%	6.7%
Pro-Forma Y-Y %			*6.7%*	*6.8%*	*5.0%*	*8.1%*			
JNJ Growth Ex-STJ	*8.1%*	*5.1%*	*6.4%*	*6.5%*	*4.6%*	*7.9%*			
Sales Growth Impact of STJ			*0.3%*	*0.3%*	*0.5%*	*0.3%*			
Profit Impact									
Total Incremental Operating Profit		976	1,104	1,229	1,385	1,572			
Merger Synergies		200	200	200	200	200			
STJ Other Expense		27	4	0	-4	-10			
Profit w/Synergies and STJ Other Expenses		1,149	1,300	1,429	1,590	1,782			
After Tax STJ Income		850	962	1,057	1,176	1,319			
Impact on JNJ Interest Income - After Tax		-489	-465	-439	-410	-378			
Net Impact on JNJ Net Profit		**361**	**497**	**619**	**766**	**941**			
	2005 E	**2006 E**	**2007 E**	**2008 E**	**2009 E**	**2010 E**	**'05-'08**	**'05-'10**	**'07-'10**
Pre STJ JNJ EPS	3.49	3.74	4.09	4.38	4.52	4.98	7.9%	7.4%	6.8%
JNJ Cash EPS with STJ		**3.67**	**4.05**	**4.36**	**4.55**	**5.04**	7.7%	7.6%	7.6%
STJ Impact on Cash EPS		-0.06	-0.04	-0.01	0.03	0.06			
Amort of Intang. Per Share (Non-Cash)		(0.14)	(0.14)	(0.14)	(0.14)	(0.14)			
JNJ GAAP EPS with STJ		$3.53	$3.91	$4.23	$4.41	$4.90			
STJ Impact on JNJ GAAP EPS		(0.20)	(0.17)	(0.15)	(0.11)	(0.08)			
Growth Impact of STJ									
Pre STJ JNJ EPS Y-Y		7.1%	9.4%	7.1%	3.3%	10.2%			
JNJ+STJ EPS ex-Amort of STJ Intangibles		5.3%	10.3%	7.8%	4.2%	10.9%			
Impact of STJ ex-Amort. of Intangibles		-1.9%	0.9%	0.7%	0.9%	0.7%			
JNJ GAAP EPS Y-Y with STJ Intangibles		1.4%	10.7%	8.1%	4.3%	11.2%			
STJ Impact on GAAP EPS Growth		-5.7%	1.3%	0.9%	1.1%	1.0%			

Assumes STJ bought at $62 per share (15% Premium to January 13 Close)
Assumes JNJ shares are worth $62.00
A Actuals
E Prudential Equity Group Estimates
Source: Prudential Equity Group, LLC, and Company Reports

Larry Biegelsen I 212 778 5825 I Lawrence_Biegelsen@prusec.com
Prudential Equity Group, LLC I One New York Plaza, 15th Floor I New York, NY 10292

Exhibit H

January 23, 2006

EDWARDS

HEALTHCARE INDUSTRY NOTE

The Game May Be Far from Over

Disclosure Information: Please see pages 5 - 12 of this report for important disclosure information.

Jan David Wald, PhD (617) 854-1968
John Boylan, *Associate Analyst* (314) 955-2395
Charlie Wang, *Associate Analyst* (617) 854-1979

HEALTH CARE

We have had conversations with Johnson & Johnson (JNJ) and Boston Scientific (BSX) and others recently that lead us to believe that the Guidant (GDT) game is far from over. Both companies seem intent on winning the battle for GDT, even to the extent of being 'nice' to sell side analysts. Our takeaway message from these conversations has been that both sides believe there is information to share that can bolster the argument for its being a better suitor for GDT.

JNJ, for example, reminded us that the analysis that BSX presented as to its valuation included price objectives that did not assume the deal had taken place. That is certainly true of our $42 price objective, which is built on our beliefs about the dynamics of the drug eluting stent market and BSX's potential pipeline of products (moving to the right in time and leaving some unsuccessful projects behind to be sure, assuming its deal with GDT goes through). Suffice it to say, we were glad that BSX did not just use our Price Objective, but averaged it with others.

We were also reminded by JNJ that it had three patents related to '-limus' compounds that it thought precluded any other company from using such a compound on a stent. We were only given two patent numbers (6776796 and 6585764), and, sure enough, both have to do with using any '-limus' on a stent. We have not vetted these patents, but they did seem quite broad in their language. When we spoke to BSX management about them, we were told neither GDT nor Abbott (ABT) seemed to be concerned about them, and that their broad language may make them non-defensible. As we said, we have not vetted them yet.

Here Are Our Initial Thoughts for Potential EPS, Assuming Things Go Through as BSX Has Planned

As for our conversation with BSX, we were surprised, somewhat, by the conservative assumptions it was making on stent market share (it was trying to keep to Street assumptions) and especially on GDT high voltage market share (we had been presuming, as has the Street, a faster ramp to normalcy). BSX is assuming that GDT only will have 26% share exiting '07, 25% in mid-'07 and 24% in 4Q06. Because of this we are assuming the company earns $0.90 in '06, $1.35 in '07, $1.80 in '08 and $2.35 in '09 on a pro forma basis, assuming the BSX/GDT merger goes through as planned. We believe the company's internal estimates are lower than these. We discuss how we derived these estimates in more detail later on in this piece

We also would like to remind investors that this analysis and all subsequent analysis on this piece are based on the assumption that BSX does indeed merge with GDT at the $80 price recently submitted by BSX. JNJ has yet to respond to this new bid by BSX and it may do so. As a result, investors should view this analysis as speculation based on what we know at this time. **Since this is speculation, we are maintaining our price objective and estimates at this time as we have no assurances that BSX will end up with GDT.** It is still a pretty dynamic atmosphere out there in our view.

Additional Synergies with BSX/GDT? Perhaps.

BSX also told us that there were more potential synergies than it had initially expected. It has said that it expected $400 million in synergies, $200 million from the GDT side and $200 million from its side, mainly from reducing corporate overhead and only having to have 1.2x the international

infrastructure that it currently has. It has also determined that there are between $50 million and $100 million of manufacturing savings that can be realized as well (especially in inspection, scrap and waste). We are not surprised by this. Our experience at GDT was that manufacturing efficiency, while taken seriously, was not taken as seriously as it has been at BSX.

As far as the arrangements with ABT is concerned (ABT, if BSX ends up with GDT, would purchase GDT's vascular business and share rights to GDT's drug eluting stent program. It also would own a portion of BSX, approximately 4%), it appears that ABT was the only true candidate for the rapid exchange technology or the larger deal that BSX is proposing. This would imply that the FTC is probably agreeable to the plan being offered, so it is more of a matter of time than worrying about the structure of the planned acquisition. We do believe that a definitive offer will likely have to be in place prior to the deal being closed. We also think that it will be late 2008/early 2009 before we see a combination product in the market.

Interesting times these.

Our Numbers Analysis, at Least on a Theoretical Basis

Now that it is BSX' turn at bat in the battle for GDT (JNJ may be heard from before Wednesday), we thought we would take a look at what BSX's value might be after any such merger. However, **investors should keep in mind once again that this exercise is theoretical**, as GDT has yet to recommend BSX's bid and we have not heard back from JNJ who, again, could come back with a new bid itself. BSX did give some level of guidance of what it might expect to see in terms of EPS after a potential merger when it bid $72 per share for GDT. At that time, BSX stated that we could expect EPS to be in a rage of $1.50 to $1.66 in 2007 and $1.98 to $2.18 in 2008.

A lot has changed since that time, however due to BSX's $80 bid for GDT. While we think BSX wisely sold some equity to Abbott (ABT) in its latest bid, which resulted in less debt being accumulated, there still should be some additional incremental debt it has taken on (around $200 million) and potential EPS dilution from those new shares being sold to ABT.

Back to the Pre-Taxus Days in Terms of Expense Control?

However, in our subsequent discussions with the company, it indicated a willingness to return to "pre-Express/Taxus" spending disciplines, assuming that it succeeds in its efforts to acquire GDT. Remember before the Express stent (the bare metal platform that BSX developed internally before the DES era), BSX was suffering from an extended period of market share losses (down to 8% of the market by our reckoning) and lackluster top line growth.

We think that cost control at this point is important. During past analyst meetings BSX indicated that it wanted to keep its after tax margins below 30% as it believed that it had a number of projects it could invest in both internally and externally (and it mentioned at the time, we think correctly, that investors would not reward it for a relatively high after tax margin). Our question is how deeply will BSX reign in costs assuming that its operations are already relatively efficient, as evidenced by operating margins often in excess of 30%? After speaking with the company on Friday, it is apparent that it does intend to slow down expenditures, because, as the management put it, now that we would have GDT's pipeline and R&D efforts, we may be able to slow down or stop expenditures related to longer-term projects. We should all remember that BSX has been spending approximately $600 million or more on milestone payments and new technology projects in addition to its in-house R&D expenditures. With a new focus, having acquired GDT, these projects will be reviewed and some of them most likely terminated.

We May See Dilution Until FY10, in This Scenario

Regardless of the synergies the company finds in these R&D programs, BSX's EPS should be diluted until FY10, at least according to our analysis and our assumptions so far. We are assuming that in the DES market that BSX retains its entire market share that we assumed it would get before the merger (approximately 30%) and we layered on top of that a portion of what we assumed would be GDT's market share. **This analysis and all subsequent analysis in this piece, again, is predicated on BSX succeeding in obtaining GDT, which we think is not a sure thing** as we have not definitively heard from JNJ as of yet.

Going into more detail, we originally assumed that GDT would also achieve approximately 30% of the DES market by the end of the decade. Taking that figure we assumed that BSX and ABT would split 40% of that market share each, with the remainder going to JNJ, due to continuity of JNJ's operations and marketing teams (sorry, MDT). The company has told us that it is assuming that two-thirds of the market share will be incrementally derived, and

one-third from cannibalization. The numbers work out to be almost equivalent. We are going to stick with our analysis. It's easier on the eyes.

We further assumed that BSX would have most of its integration issues behind it by late FY08 to early FY09 with its operating margins starting to return to normalcy (30%+). The company is actually more conservative and assumes that it will not reach that goal until close to FY10. We are also assuming that GDT's CRM group slowly returns to close to a 30% market share range in high voltage in the United States by the end of the decade. However, due to GDT related debt, integration costs and additional shares that BSX has offered, it emerges from earnings dilution around FY10 in our model. Preliminarily, we assume that BSX's pro-forma earnings may approximate $0.90 for FY06, $1.35 for FY07, $1.80 for FY08 and $2.35 for FY09. Once again, this is predicated on the assumption that BSX acquires GDT, and all of this analysis may change quickly if JNJ comes in with a competing bid.

Here's Our Initial Take on a Theoretical Valuation, But the Game Might Not Be Over Yet. Keeping those assumptions and qualifiers in mind, recently our peer group average for BSX (MDT, EW, STJ) was trading at a one year forward multiple of 25.6x. The question we believe worth asking, is what should be the discount to that multiple? Using that average with no discount leads us to a valuation of $35 per share, utilizing our preliminary FY07 estimate. We decided to use FY07 as opposed to the one year forward (FY06) as FY07 would be the first full fiscal year with GDT under its belt as well as the first year it may begin to move toward normalcy. However, we do believe that BSX should receive some discount due to the potentially higher short-term financial risk the company might face. The problem is that we cannot think of any recent acquisitions of this size and scope among equals that is dilutive over the course of a couple years in this or any other industry. Therefore any number we pick as a discount rate would be somewhat arbitrary.

Since we were unsure on what discount to that multiple should be, we decided to create a table of discount values to determine a valuation range and then make an more educated estimate on what a potential valuation might be using our recent comp group EPS multiple of 25.6x as a base.

	Discount Rates			
EPS Ests	10%	20%	30%	40%
$1.15	$26.50	$23.55	$20.61	$17.66
$1.25	$28.80	$25.60	$22.40	$19.20
$1.35	$31.10	$27.65	$24.19	$20.74
$1.45	$33.41	$29.70	$25.98	$22.27
$1.55	$35.71	$31.74	$27.78	$23.81

Source: A.G. Edward theoretical estimates.

Using the middle portion of this table as a proxy for potential outcomes, we see a range of potential values of $30 to $22 per share. This fits in within our preliminary pro-forma discounted cash flow analysis of approximately $28 per share. In that analysis, we used all of the EPS assumptions listed above as well as weighted average cost of capital of 12.0%, an implied market risk for the shares of 10.5% (our large cap universe range is 7.5% to 11.0%) and a long-term growth rate of 12%.

However, we would also like to stress that this is a preliminary analysis. We expect to see and hear more from BSX, GDT and possibly JNJ in the coming days. Our intention is to give investors an idea of what might be, given events could change very quickly. Importantly, we are sticking with ourl price objective for BSX of $42 per share and our current estimates as we do not believe this saga is near completion at this time.

Boston Scientific (BSX – $23.34 – Buy/Aggressive) Valuation
We use a three-stage discounted cash flow model, which leads us to a price objective of $42 per share. Our weighted average cost of capital was 11.3%. Our market risk premium is 9%. We assumed a free cash flow growth rate of 11.75% for 10 years after our detailed cash flow model ends in 2010 and assume a growth rate of 4% thereafter. On a P/E basis, BSX's one-year forward P/E five-year average is 28.8x with a range of 70.7x to 12.0x. Based upon our FY06 estimate of $1.82 and our price objective of $42, we have a target P/E value of 23.0x, a discount to its five-year average, but appropriate in our opinion as we think BSX has a good long-term pipeline.

BSX Risks To Valuation
Risk to achieving our price objective include unanticipated market share losses in the drug-eluting stent market (e.g., new competitive products being more successful than we anticipate, product recalls, etc.), new products not being successfully brought to market or not experiencing sales levels as highs as we anticipate, regulatory risk (e.g., reimbursement and regulatory approval), ongoing

litigation risk and the highly competitive markets in which the company competes.

Guidant (GDT – $76.00 – Hold/Speculative)
Valuation
We use a three stage discounted cash flow model for our valuation. Our discount rate on our future cash flows, which is the weighted average cost of capital, we are using is 12.1%. This and other assumptions lead us to believe GDT is at fair value. Based upon our FY06 estimate of $1.70 per share, GDT is now trading at a P/E multiple of 44.8x.

GDT Risks To Valuation
The ongoing issues and uncertainties we have seen in the stent business are the major risks for Guidant. Others include acquisition risks, slower than expected uptake of CHF devices, new technology not only from direct competitors, but also from other sectors as well such as Pharma, regulatory risk, reimbursement risk and litigation risk.

Johnson & Johnson (JNJ – $61.19 – Hold/Conservative) Valuation
We utilize a three-stage discounted cash flow analysis for our valuation methodology. Our weighted average cost of capital assumption at the time of analysis was 10.4%, we assumed a free cash flow growth rate of 9.0% for 10 years after our detailed forecasts embedded in our model end in FY10, and 4.0% thereafter. These and other assumptions lead us to believe that the shares are at a level that represents what we would consider fair value. On a P/E basis, JNJ's two-year forward P/E five-year average is 20.0x with a range of 27.7x to 15.2x. Based upon our FY06 estimate of $3.80, JNJ is currently trading at a P/E (at a recent price of $61.19 per share) of 16.1x. We believe that a multiple at the lower end of the range is justified due to competition in the drug-eluting stent marketplace, and potential and existing generic competition in some product lines in pharma.

JNJ Risks To Valuation
Johnson & Johnson may see greater competition than expected in the drug-eluting stents market in the United States, and new drug-eluting stent products from competitors in Europe. The Pharma pipeline may be weaker than expected, and there may be increased competition from generic manufacturers.

Abbott Labs (ABT – $40.51 – Buy/Aggressive)
Valuation
We utilize a three-stage discounted cash flow analysis for our valuation methodology. Our weighted average cost of capital assumption is 11.5% and our risk premium assumption is 9%. Our out year operating cash flow growth assumption is 11.0% for ten years (2011-2020)-right in the middle of the largest of our large-cap group. These and other assumptions lead us to our price objective of $46 per share. On a P/E basis, using our $2.70 FY06 EPS estimate, and our $46 price objective the multiple is 17.0x. This compares to a five-year historical two-year forward P/E average of 18.3x, with a range of 13.4x to 25.2x. We feel that our implied target multiple, which is close to its historical average, is justified due to uncertainty concerning generic competition, but offset by good potential we see in Medical Products. Therefore, being close to the middle seems like a good place to be.

ABT Risks To Valuation
Risks to achieving our price objective include the fact that Abbott's pharmacological pipeline may not be as robust as we have assumed, sales of its key products (such as Humira) may not be as strong as we anticipate and it participates in highly competitive and regulated markets.

Analyst Certification Statement
The views expressed in this research report accurately reflect my personal views about the subject company/companies and securities. I receive no compensation that is directly or indirectly related to the specific recommendations or views contained within this report.

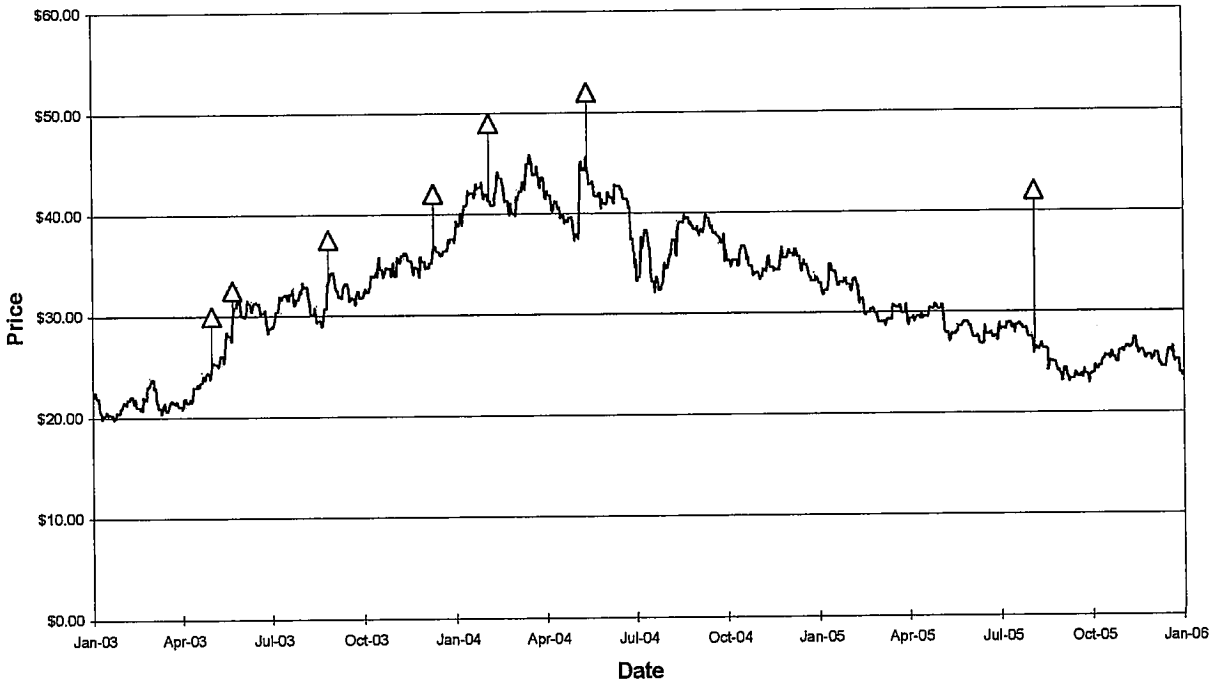
All prices from intraday on 1/230/6.

BOSTON SCIENTIFIC

EDWARDS.

January 21, 2006
Buy/Aggressive
BSX/NYSE/$23.59

Price Objective: $42.00



Pricing sources: Factset and IDSI

PRICE OBJECTIVE (PO) CHANGES *

Date	Closing Price	PO	Date	Closing Price	PO	Date	Closing Price	PO
		25.00	09/16/2003	33.25	37.50	06/02/2004	44.70	52.00
05/21/2003	25.04	30.00	12/30/2003	36.54	42.00	08/24/2005	26.38	42.00
06/11/2003	29.88	32.50	02/24/2004	41.27	49.00			

* NA: Positive rating removed; no price objective supplied.

RATING/SUITABILITY CHANGES

Date	Closing Price	Rating/Suitability	Date	Closing Price	Rating/Suitability
		Strong Buy/Aggressive			

ANALYST COVERAGE CHANGES

Analyst	From	To	Analyst	From	To
Jan D. Wald	01/18/2001				

BOSTON SCIENTIFIC

EDWARDS

January 21, 2006

Buy/Aggressive

BSX/NYSE/$23.59 **Price Objective: $42.00**

Rating	Master List Companies	Current Rating Distribution	Past 12 months Investment Banking Clients	Past 12 months % of Investment Banking Clients *
Buy	257	36%	48	19%
Hold/Neutral	440	62%	28	6%
Sell	12	2%	0	0%

* Percentage of Investment Banking Clients on Master List by rating.

OUR 3-TIER RATING SYSTEM (12-18 month time horizon)

Buy: A total return is anticipated in excess of the market's long-term historic rate (approximately 10%). Total return expectations should be higher for stocks which possess greater risk.

Hold: Hold the shares, with neither a materially positive total return nor a materially negative total return is anticipated.

Sell: Stock should be sold, as a materially negative total return is anticipated.

RISK SUITABILITY (Relates to fundamental risk, including earnings predictability, balance sheet strength and price volatility)

Conservative: Fundamental risk approximates or is less than the market.

Aggressive: Fundamental risk is higher than the market.

Speculative: Fundamental risk is significantly higher than the market.

The suitability ratings assigned by A.G. Edwards industry analysts to individual securities should be reviewed by investors and their financial consultants to determine whether a particular security is suitable for their portfolio, with full consideration given to existing portfolio holdings.

COMPANY SPECIFIC DISCLOSURES:
Analyst or household member owns a long common equity position.
AGE and/or officer(s) own a long position in the issuer's equity securities.

The views expressed in this research report accurately reflect my personal views about the subject company and its securities.

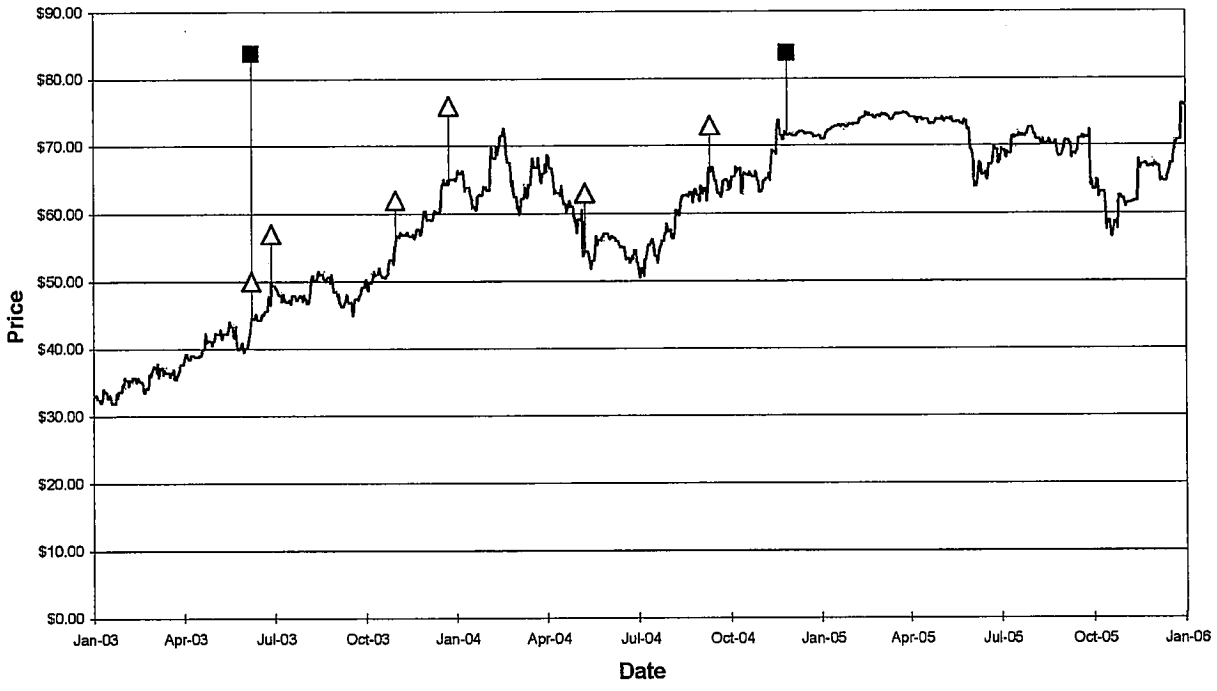
AGE's research analysts receive no compensation in connection with the firm's investment banking business. The analyst certifies that he/she receives no compensation that is directly or indirectly related to the specific recommendations or views contained within this report. Analysts may be eligible for annual bonus compensation based on the overall profitability of the firm, which takes into account revenues derived from all of the firm's business activities, including its investment banking business.

Price objectives and recommendations contained in this report are based on a time horizon of 12-18 months, but there is no guarantee the objective will be achieved within the specified time horizon. Price objectives are determined by a subjective review of fundamental and/or quantitative characteristics of the issuer and the security that is the subject of this report. A variety of methods may be used to determine the value of a security including, but not limited to, discounted cash flow, peer group comparisons, sum of the parts and enterprise values. All securities are subject to market, interest rate and general economic risks. Specific information is provided in the text of our most recent research report.

GUIDANT CORP

EDWARDS

January 21, 2006
Hold/Speculative
GDT/NYSE/$75.95



Pricing sources: Factset and IDSI

PRICE OBJECTIVE (PO) CHANGES *

Date	Closing Price	PO	Date	Closing Price	PO	Date	Closing Price	PO
		NA	11/20/2003	55.35	62.00	09/30/2004	66.04	73.00
06/27/2003	44.51	50.00	01/13/2004	64.28	76.00	12/17/2004	71.62	NA
07/17/2003	49.96	57.00	05/28/2004	54.34	63.00			

* NA: Positive rating removed; no price objective supplied.

RATING/SUITABILITY CHANGES

Date	Closing Price	Rating/Suitability	Date	Closing Price	Rating/Suitability
		Hold/Speculative	12/17/2004	71.62	Hold/Speculative
06/27/2003	44.51	Buy/Speculative			

ANALYST COVERAGE CHANGES

Analyst	From	To	Analyst	From	To
Jan D. Wald	01/08/2001				

GUIDANT CORP

EDWARDS

January 21, 2006

Hold/Speculative

GDT/NYSE/$75.95

Rating	Master List Companies	Current Rating Distribution	Past 12 months Investment Banking Clients	Past 12 months % of Investment Banking Clients *
Buy	257	36%	48	19%
Hold/Neutral	440	62%	28	6%
Sell	12	2%	0	0%

* Percentage of Investment Banking Clients on Master List by rating.

OUR 3-TIER RATING SYSTEM (12-18 month time horizon)

Buy: A total return is anticipated in excess of the market's long-term historic rate (approximately 10%). Total return expectations should be higher for stocks which possess greater risk.

Hold: Hold the shares, with neither a materially positive total return nor a materially negative total return is anticipated.

Sell: Stock should be sold, as a materially negative total return is anticipated.

RISK SUITABILITY (Relates to fundamental risk, including earnings predictability, balance sheet strength and price volatility)

Conservative: Fundamental risk approximates or is less than the market.

Aggressive: Fundamental risk is higher than the market.

Speculative: Fundamental risk is significantly higher than the market.

The suitability ratings assigned by A.G. Edwards industry analysts to individual securities should be reviewed by investors and their financial consultants to determine whether a particular security is suitable for their portfolio, with full consideration given to existing portfolio holdings.

COMPANY SPECIFIC DISCLOSURES:
Analyst or household member owns a long common equity position.

The views expressed in this research report accurately reflect my personal views about the subject company and its securities.

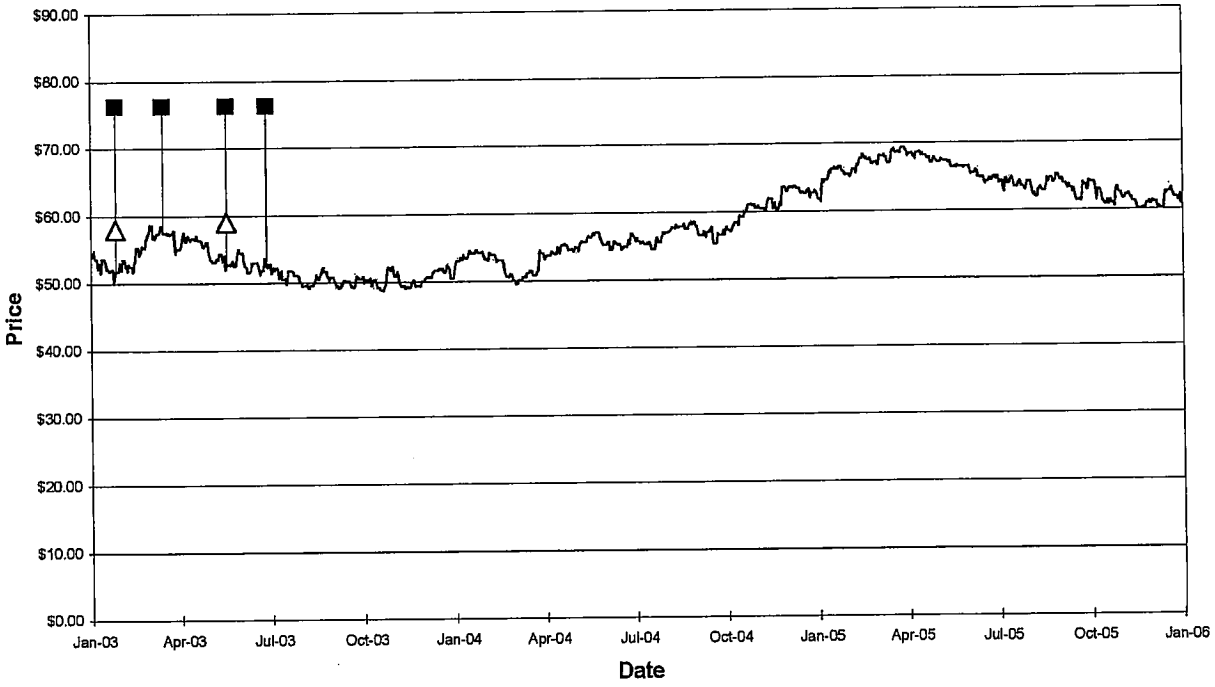
AGE's research analysts receive no compensation in connection with the firm's investment banking business. The analyst certifies that he/she receives no compensation that is directly or indirectly related to the specific recommendations or views contained within this report. Analysts may be eligible for annual bonus compensation based on the overall profitability of the firm, which takes into account revenues derived from all of the firm's business activities, including its investment banking business.

Price objectives and recommendations contained in this report are based on a time horizon of 12-18 months, but there is no guarantee the objective will be achieved within the specified time horizon. Price objectives are determined by a subjective review of fundamental and/or quantitative characteristics of the issuer and the security that is the subject of this report. A variety of methods may be used to determine the value of a security including, but not limited to, discounted cash flow, peer group comparisons, sum of the parts and enterprise values. All securities are subject to market, interest rate and general economic risks. Specific information is provided in the text of our most recent research report.

JOHNSON & JOHNSON

EDWARDS.

January 21, 2006
Hold/Conservative
JNJ/NYSE/$60.80



Pricing sources: Factset and IDSI

PRICE OBJECTIVE (PO) CHANGES *

Date	Closing Price	PO	Date	Closing Price	PO	Date	Closing Price	PO
		NA	04/03/2003	57.46	NA	07/16/2003	52.60	NA
02/14/2003	51.75	58.00	06/06/2003	52.75	59.00			

* NA: Positive rating removed; no price objective supplied.

RATING/SUITABILITY CHANGES

Date	Closing Price	Rating/Suitability	Date	Closing Price	Rating/Suitability
		Hold/Conservative	06/06/2003	52.75	Buy/Conservative
02/14/2003	51.75	Buy/Conservative	07/16/2003	52.60	Hold/Conservative
04/03/2003	57.46	Hold/Conservative			

ANALYST COVERAGE CHANGES

Analyst	From	To	Analyst	From	To
Jan D. Wald	08/17/2001				

JOHNSON & JOHNSON

EDWARDS

January 21, 2006

Hold/Conservative

JNJ/NYSE/$60.80

Rating	Master List Companies	Current Rating Distribution	Past 12 months Investment Banking Clients	Past 12 months % of Investment Banking Clients *
Buy	257	36%	48	19%
Hold/Neutral	440	62%	28	6%
Sell	12	2%	0	0%

* Percentage of Investment Banking Clients on Master List by rating.

OUR 3-TIER RATING SYSTEM (12-18 month time horizon)

Buy: A total return is anticipated in excess of the market's long-term historic rate (approximately 10%). Total return expectations should be higher for stocks which possess greater risk.

Hold: Hold the shares, with neither a materially positive total return nor a materially negative total return is anticipated.

Sell: Stock should be sold, as a materially negative total return is anticipated.

RISK SUITABILITY (Relates to fundamental risk, including earnings predictability, balance sheet strength and price volatility)

Conservative: Fundamental risk approximates or is less than the market.

Aggressive: Fundamental risk is higher than the market.

Speculative: Fundamental risk is significantly higher than the market.

The suitability ratings assigned by A.G. Edwards industry analysts to individual securities should be reviewed by investors and their financial consultants to determine whether a particular security is suitable for their portfolio, with full consideration given to existing portfolio holdings.

COMPANY SPECIFIC DISCLOSURES:
Analyst or household member owns a long common equity position.
AGE or an affiliate received compensation from the subject company for products or services other than investment banking services during the past 12 months, and analyst or person with ability to influence substance of this report is aware of same.
The subject company is or was a client of AGE during the past 12 months for non-investment banking securities-related services and analyst is aware of same.
AGE and/or officer(s) own a long position in the issuer's equity securities.

The views expressed in this research report accurately reflect my personal views about the subject company and its securities.

AGE's research analysts receive no compensation in connection with the firm's investment banking business. The analyst certifies that he/she receives no compensation that is directly or indirectly related to the specific recommendations or views contained within this report. Analysts may be eligible for annual bonus compensation based on the overall profitability of the firm, which takes into account revenues derived from all of the firm's business activities, including its investment banking business.

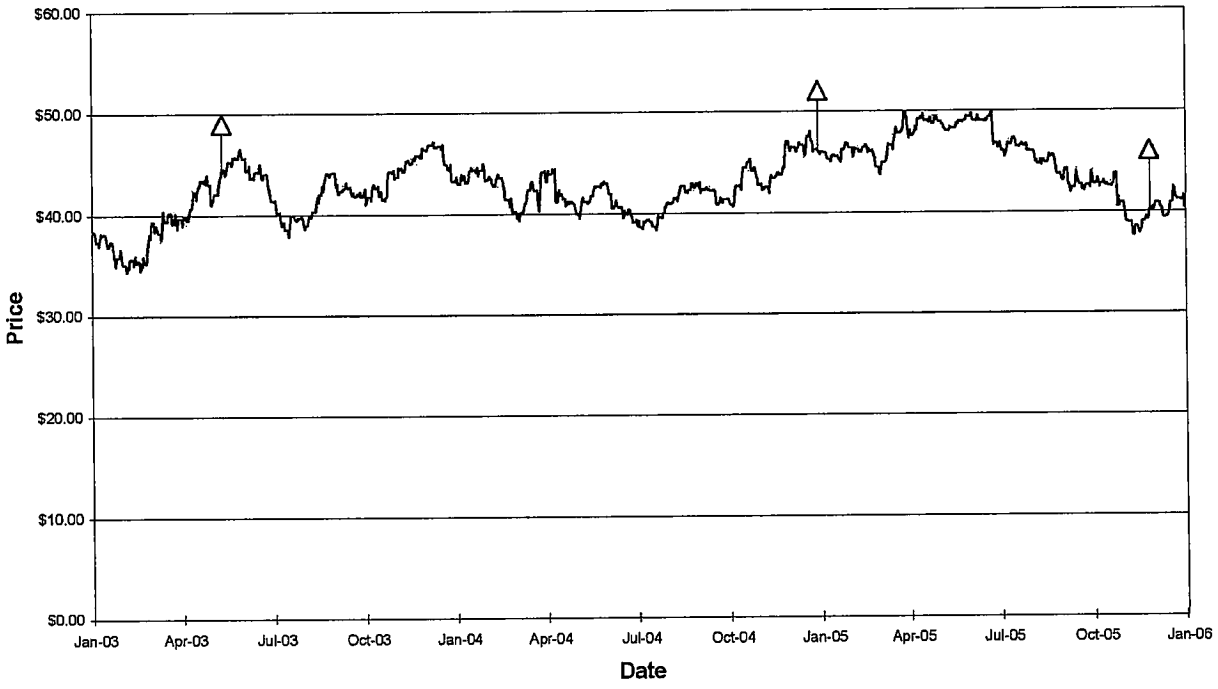
Price objectives and recommendations contained in this report are based on a time horizon of 12-18 months, but there is no guarantee the objective will be achieved within the specified time horizon. Price objectives are determined by a subjective review of fundamental and/or quantitative characteristics of the issuer and the security that is the subject of this report. A variety of methods may be used to determine the value of a security including, but not limited to, discounted cash flow, peer group comparisons, sum of the parts and enterprise values. All securities are subject to market, interest rate and general economic risks. Specific information is provided in the text of our most recent research report.

ABBOTT LABORATORIES

EDWARDS

January 21, 2006
Buy/Aggressive
ABT/NYSE/$40.35

Price Objective: $46.00



Pricing sources: Factset and IDSI

PRICE OBJECTIVE (PO) CHANGES *

Date	Closing Price	PO	Date	Closing Price	PO	Date	Closing Price	PO
		46.00	01/18/2005	46.04	52.00			
05/30/2003	44.55	49.00	12/16/2005	40.17	46.00			

* NA: Positive rating removed; no price objective supplied.

RATING/SUITABILITY CHANGES

Date	Closing Price	Rating/Suitability	Date	Closing Price	Rating/Suitability
		Buy/Aggressive			

ANALYST COVERAGE CHANGES

Analyst	From	To	Analyst	From	To
Jan D. Wald	08/17/2001				

ABBOTT LABORATORIES

EDWARDS

January 21, 2006
Buy/Aggressive
ABT/NYSE/$40.35 Price Objective: $46.00

Rating	Master List Companies	Current Rating Distribution	Past 12 months Investment Banking Clients	Past 12 months % of Investment Banking Clients *
Buy	257	36%	48	19%
Hold/Neutral	440	62%	28	6%
Sell	12	2%	0	0%

* Percentage of Investment Banking Clients on Master List by rating.

OUR 3-TIER RATING SYSTEM (12-18 month time horizon)

Buy: A total return is anticipated in excess of the market's long-term historic rate (approximately 10%). Total return expectations should be higher for stocks which possess greater risk.

Hold: Hold the shares, with neither a materially positive total return nor a materially negative total return is anticipated.

Sell: Stock should be sold, as a materially negative total return is anticipated.

RISK SUITABILITY (Relates to fundamental risk, including earnings predictability, balance sheet strength and price volatility)

Conservative: Fundamental risk approximates or is less than the market.

Aggressive: Fundamental risk is higher than the market.

Speculative: Fundamental risk is significantly higher than the market.

The suitability ratings assigned by A.G. Edwards industry analysts to individual securities should be reviewed by investors and their financial consultants to determine whether a particular security is suitable for their portfolio, with full consideration given to existing portfolio holdings.

COMPANY SPECIFIC DISCLOSURES:
Not applicable.

The views expressed in this research report accurately reflect my personal views about the subject company and its securities.

AGE's research analysts receive no compensation in connection with the firm's investment banking business. The analyst certifies that he/she receives no compensation that is directly or indirectly related to the specific recommendations or views contained within this report. Analysts may be eligible for annual bonus compensation based on the overall profitability of the firm, which takes into account revenues derived from all of the firm's business activities, including its investment banking business.

Price objectives and recommendations contained in this report are based on a time horizon of 12-18 months, but there is no guarantee the objective will be achieved within the specified time horizon. Price objectives are determined by a subjective review of fundamental and/or quantitative characteristics of the issuer and the security that is the subject of this report. A variety of methods may be used to determine the value of a security including, but not limited to, discounted cash flow, peer group comparisons, sum of the parts and enterprise values. All securities are subject to market, interest rate and general economic risks. Specific information is provided in the text of our most recent research report.

Additional information available upon request. With the exception of information about A.G. Edwards & Sons, Inc., the material contained herein has been prepared from sources and data we believe to be reliable but we make no guarantee as to its accuracy or completeness. This material is published solely for informational purposes and is not an offer to buy or sell or a solicitation of an offer to buy or sell any security or investment product. This material is not to be construed as providing investment services in any jurisdiction where such offers or solicitation would be illegal. Opinions and estimates are as of a certain date and subject to change without notice. You should be aware that investments can fluctuate in price, value and/or income, and you may get back less than you invested. Past performance is not necessarily a guide to future performance. Investments or investment services mentioned may not be suitable for you and if you have any doubts you should seek advice from your financial consultant. Where the purchase or sale of an investment requires a change from one currency to another, fluctuations in the exchange rate may have an adverse effect on the value, price or income of the investment. Certain investments may be mentioned that are not readily realizable. This means that it may be difficult to sell or realize the investment or obtain reliable information regarding its value. The levels and basis of taxation can change.

This document has been approved by A.G. Edwards & Sons (U.K.) Limited, authorized and regulated by the Financial Services Authority.

 www.agedwards.com

Exhibit I

citigroup

See page 8 for Analyst Certification and Important Disclosures

Multi-Company Note

Medical Supplies & Technology

An INTERESTing New Offer

January 13, 2006

[redacted]
Matthew J Dodds

Efrem Kamen

SUMMARY

- BSX's new bid appears more focused on anti-trust issues than a higher price, which is likely to be based on intellectual property as much as timing. We don't think BSX's new offer is enough to get GDT to switch sides.
- A BSX/GDT deal may not have the freedom of passage through the FTC that is widely anticipated, as JNJ holds some key intellectual property needed to make ABT a "competitive" DES player.
- JNJ owns the IP around the use of the drug sirolimus (rapamycin) and its analogues on a stent - this includes both ABT-578 and everolimus.
- When the FTC initially approved JNJ/GDT in October, JNJ agreed to license rapid exchange and other stent rights to ABT. We suspect that the other stent rights included the IP surrounding the use of rapamycin analogues on a stent.
- Without this IP, the FTC could have concern over ABT's ability to make ZoMaxx or Xience V a viable competitor.

United States

SUMMARY VALUATION AND RECOMMENDATION DATA

Company (Ticker)	Price	Expected Returns Price	Div.	Total		Rating	Div.(E)	Target	LTGR	Earnings Per Share Current Yr	Next Yr
Abbott Laboratories- (ABT)	$41.34	(8.1%)	2.6%	(5.5%)	Curr	3M	$1.07	$38.00	7%	$2.48E	$2.50E
					Prev	3M	$1.07	$38.00	7%	$2.48E	$2.50E
Boston Scientific- (BSX)	$25.05	7.8%	0.0%	7.8%	Curr	2H	$0.00	$27.00	7%	$1.83E	$1.80E
					Prev	2H	$0.00	$27.00	7%	$1.83E	$1.80E
Guidant Corporation- (GDT)	$70.40	(31.8%)	0.6%	(31.3%)	Curr	3H	$0.40	$48.00	15%	$1.82E	$1.49E
					Prev	3H	$0.40	$48.00	15%	$1.82E	$1.49E
Johnson & Johnson- (JNJ)	$62.21	28.6%	2.1%	30.7%	Curr	1L	$1.29	$80.00	11%	$3.50E	$3.86E
					Prev	1L	$1.29	$80.00	11%	$3.50E	$3.86E

OPINION

BSX's new offer shows GDT's Board is as concerned with anti-trust as price...

After the close yesterday, Boston came back with another offer for Guidant. While this was widely anticipated, it is a bit quicker than we thought and the structure puts more of a focus on anti-trust concerns than a pricing premium. Specifically, the Boston offer of $73 is only $1 higher than the last offer and is still equally split between stock and cash. We felt Boston would go to $76 with its follow up bid on the chance that JNJ was "maxed" at $68. In addition to the $1 increase in price, Boston has altered its agreement on two fronts to address two apparent concerns of Guidant's Board: 1) the ability to get through the FTC, and 2) the ability to close the deal in a timely manner. To address these concerns, Boston has now

citigroup

offered to divest all overlapping assets if necessary and will pay $0.012 in cash per day (or $4MM per day) for every day the closing slips after April 1.The second component is quite novel, and we aren't sure if this has ever been done before in a major acquisition/merger. While it may sound lucrative since the cash register rings daily, it's really quite small ($120MM a month) in relation to the $25B deal size.

...And could be related to JNJ's IP around using limus compounds on a stent...

The interesting new features of Boston's offer implies that Guidant's Board is more concerned with anti-trust issues than the investment community has realized. Our recent work in the area suggests there may be one major issue that has been overlooked to date – JNJ's IP position on using sirolimus (rapamycin) and its analogues on a stent. JNJ licensed rapamycin from Wyeth but also has its own patents that cover the use of rapamycin and rapamycin analogues on a stent. These patents include the '796 patent filed in May 2001 and the '536 patent filed in April 2003. The patents have never been challenged or enforced because no other company has launched a limus-based drug-eluting stent in the US, but are likely to eventually lead to litigation. While we have not done specific research on the strength of the patents, the claims appear to somewhat broadly cover the use of rapamycin on a stent to treat restenosis.

What makes this issue interesting is that JNJ is likely to have offered a license to these patents along with rapid-exchange to Abbott since ABT-578 (the drug Abbott uses for ZoMaxx) is a rapamycin analogue. If this is correct, it means that the FTC required this access to ensure that Abbott would not face litigation from JNJ when it eventually enters the US market.

...Which would remain an issue with Boston's new offer...

In the Boston deal for Guidant, neither Boston nor Abbott would garner access to the limus patents so another competitive stent entrant may not technically be "created" with this deal. (It could be argued that Guidant didn't have access to these patents before the JNJ offer, but if the FTC determined it was an issue in its JNJ/GDT review, its on the map.) Hence, while the Boston/Abbott deal looks quite a bit more comprehensive than the JNJ/Abbott deal, the importance of the limus patent rights appear to have been underestimated.

...Along with some other potential snags....

While Boston is now saying it will divest all required assets – which would presumably include dropping the "shared" rights to everolimus – this would require another "agreement" with Abbott since the current one does not include this scenario. It was also noted by the *Wall Street Journal* that Boston's last trip to the FTC was ugly as its acquisition of Cardiovascular Imaging Systems included an agreement with Hewlett Packard that the FTC felt was not honored. Finally, Boston has said little about EU anti-trust clearance, which may not be on fast-track status given that Boston and Guidant have more overlap and the EU authorities raised several product issues between JNJ and Guidant that the FTC did not raise.

...So the bottom line on the new offer is: we just don't think it's enough.

Last night, Guidant's Board noted that it will look at and respond to the new offer by Boston Scientific. Even with the new components of the Boston offer, we don't think Guidant's Board will get comfortable enough with the aforementioned anti-trust issues and the extra $1. Boston is demanding that Guidant's Board respond by 4 p.m. EST today (which is ironically Friday the 13th). If Guidant doesn't take the offer (80%), Boston could still go higher on price since Guidant's Board appeared comfortable to go with Boston earlier this week when the spread was $8. If Guidant does take Boston's new offer (20%), its hard to

citigroup

say what JNJ will do, especially given the fact that we have been incorrect on JNJ's last three moves relating to Guidant.

QUARTERLY ESTIMATES PER SHARE DATA

		Current Year		Next Year		Next Year + 1	
Ticker	Period	Current	Previous	Current	Previous	Current	Previous
ABT	1Q	$0.58A	$0.58A	$0.58E	$0.58E	NA	NA
(FYE Dec)	2Q	$0.58A	$0.58A	$0.62E	$0.62E	NA	NA
	3Q	$0.58A	$0.58A	$0.60E	$0.60E	NA	NA
	4Q	$0.74E	$0.74E	$0.70E	$0.70E	NA	NA
	Year	$2.48E	$2.48E	$2.50E	$2.50E	$2.62E	$2.62E
BSX	1Q	$0.51A	$0.51A	$0.47E	$0.47E	NA	NA
(FYE Dec)	2Q	$0.48A	$0.48A	$0.45E	$0.45E	NA	NA
	3Q	$0.42A	$0.42A	$0.42E	$0.42E	NA	NA
	4Q	$0.42E	$0.42E	$0.46E	$0.46E	NA	NA
	Year	$1.83E	$1.83E	$1.80E	$1.80E	$1.99E	$1.99E
GDT	1Q	$0.65A	$0.65A	NA	NA	NA	NA
(FYE Dec)	2Q	$0.63A	$0.63A	NA	NA	NA	NA
	3Q	$0.28A	$0.28A	NA	NA	NA	NA
	4Q	$0.26E	$0.26E	NA	NA	NA	NA
	Year	$1.82E	$1.82E	$1.49E	$1.49E	$2.42E	$2.42E
JNJ	1Q	$0.97A	$0.97A	$1.04E	$1.04E	NA	NA
(FYE Dec)	2Q	$0.93A	$0.93A	$1.01E	$1.01E	NA	NA
	3Q	$0.87A	$0.87A	$0.97E	$0.97E	NA	NA
	4Q	$0.74E	$0.74E	$0.83E	$0.83E	NA	NA
	Year	$3.50E	$3.50E	$3.86E	$3.86E	$4.22E	$4.22E

VALUATION AND RISKS – COMPANIES DISCUSSED

Johnson & Johnson (JNJ –$62.21; 1L)

Valuation

We arrive at our $80 target price for Johnson & Johnson based on an average of three different valuations: 1) a 21x multiple off our forward 12 months (F12M) EPS forecast; 2) a TEV/2005E EBITDA target multiple of 14x; and 3) a 10-year DCF analysis.

A 21x P/E multiple represents a weighted multiple using a sum-of-the-parts analysis on JNJ's three major divisions: Pharmaceuticals (58% of operating profit), MD&D (31%), and Consumer (11%). For Pharmaceuticals, our target multiple of 20x represents a modest premium to the large-cap pharmaceutical group average of 17x, but is in line to slightly above the better-positioned franchises of Eli Lilly (21x), and Novartis (18x). Our comp group also includes companies such as Bristol Myers. The range of this comp group is from 15x–19x.

For MD&D, our target multiple of 25x represents a 10% premium to our F12M forecast for the CMTI as JNJ's business should grow 16% in 2005E, well north of the group average. The group in comprised of 17 large-cap med tech companies and includes companies such as

citigroup

Medtronic, Abbott Laboratories, and Alcon. The trading range for the comp group is 15x–33x forward 12-month EPS.

For Consumer, we are forecasting a 21x multiple, which is in line with the average F12M P/E multiple the Citigroup Home & Personal Care Products Team is forecasting for the four closest comparable companies. The range of the comps group is 18x-21x and includes companies such as Avon Products, Procter & Gamble, and Colgate-Palmolive.

For our TEV/2005E EBITDA calculation, we use the 2004 share count and net debt, and the 2005E EBITDA to calculate the current multiple of 14x. Our TEV/EBITDA premium is based on the same factors as our Price/F12M EPS target, and we arrive at a TEV/EBITDA target price of $78. The range of our TEV/EBITDA for the comp groups ranges from 10x to 32x 2005 EBITDA.

Johnson & Johnson Valuation Ratios

	Current	CMTI	Hos. Sup. Peers	Pharma Peers	S&P 500	Multiple Target	Target Price	Total Return
LT EPS Growth	10%	15%	13%	9%	7%			
Price/F12M EPS	17x	23x	18x	17x	18x	21x	$78.96	26%
TEV/2004 EBITDA	11x	17x	12x			14x	$78.08	25%
Implied DCF Value	--						$84.15	35%
Derived Price Target							$80.40	29%
Dividend Yield								2%
Expected Total Return								31%

Source: Citigroup Investment Research estimates

Our DCF valuation of $84 per share is based on ten years of projected free cash flow with a 1% terminal growth rate. For an equity risk premium we used 3.8%; our adjusted beta is 0.58; and our weighted average cost of capital is 6.4%.

Risks

We rate Johnson & Johnson Low Risk based on three factors: 1) Johnson & Johnson's broad business mix in three large, defensive markets – pharmaceuticals, medical products, and consumer products – makes Johnson & Johnson the most diversified large-cap company in the health care space; 2) Johnson & Johnson is a major player in all three of its targeted markets, including the No. 1 position in the $224 billion medical products market; and 3) Johnson & Johnson has a sizable cash hoard – over $7 billion in net cash – and free cash flow generation currently running at roughly $1.5 billion/quarter.

Risks to our thesis include: 1) unexpected generic competition for Levaquin, Risperdal, Aciphex, Topamax, or Procrit before 2008; 2) the inability to gain further share in the US drug eluting stent market in 2005 and 2006; 3) overly aggressive growth expectations for Natrecor, Remicade, or Topamax; 4) issues related to the Guidant merger.

Given the recent heightened scrutiny over drug-safety, there also exists the risk that any of Johnson & Johnson major pharmaceuticals could face slowing sales because of new or increased safety concerns.

Investment risks relating to the medical supplies and technology ("med tech") industry include: 1) modest pricing pressure across most major product lines; 2) a reduction in sales and EPS benefit from foreign exchange based on favorable yoy comparisons of the U.S. dollar versus the Euro and Yen declining in 2005; and 3) a strengthening US economy could lead to a negative sector rotation, as the med-tech industry is non-cyclical in nature.

citigroup

If the impact on the company from any of these factors proves to be greater/less than we anticipate, it may prevent the stock from achieving our target price or could cause our target price to be materially outperformed.

Guidant (GDT –$70.40; 3H)

Valuation

Our $48 target on GDT is still based on fundamental valuation and not on the newly proposed deal terms by either JNJ or BSX. Our target is based on an average of a 22x P/E multiple off of our forward 12-month EPS estimate of $1.46 (Q4:05 – Q3:06), a 16x TEV/2005 EBITDA multiple, and a DCF valuation.

Our P/E multiple is based on GDT trading at 22x forward 12-month earnings, which is based on a multiple that is in line to slightly below our Citigroup Med Tech Index (CMTI) of 17 large-cap companies, which also averages 22x.. Our index includes companies such as Medtronic, Baxter, and Alcon. Our in-line target is based on Guidant performance over the next 12-months falling right in the average range of the group. The P/E multiples in the group range from as low as 15x forward earnings to as high as 33x forward earnings.

Our TEV/EBITDA multiple of 16x 2005 EBITDA is also roughly in line with the CMTI average of 17x. This is based on the same reasons as the in-line P/E multiple. The group TEV/EBITDA multiples in the CMTI range from 10x to 32x.

Guidant Estimated Valuation Ratios If JNJ or BSX Deal Breaks

	Current	CMTI	Cardio Peers	S&P 500	Multiple Target	Target Price	Total Return
Price/F12M EPS	34x	22x	26x	18x	22x	$45.04	-36%
TEV/EBITDA	17x	17x	20x		16x	$50.84	-28%
Implied DCF Value	--					$47.81	-32%
Derived Price Target						$47.89	-32%
Dividend Yeild							1%
Expected Total Return							-32%

Source: Citigroup Investment Research

Our DCF valuation of $48 per share is based on ten years of projected free cash flow with a 2% terminal growth rate. For an equity risk premium we used 3.8%; our adjusted beta is 0.79; and our weighted average cost of capital is 7.2%.

Risks

We rate Guidant High Risk primarily based on four factors: 1) Risk of failure of the company's DES programs; 2) Liability surrounding EVT; 3) Additional fallout from the ICD recall; and 4) A formal SEC investigation.

Upside investment risks to our Sell rating and target price include: 1) the completion of the proposed acquisition by either Johnson & Johnson or Boston Scientific, or 2) a stronger-than-anticipated return in the ICD market.

Investment risks relating to the medical supplies and technology ("med tech") industry include: 1) modest pricing pressure across most major product lines; 2) a reduction in sales and EPS benefit from foreign exchange if favorable yoy comparisons of the US dollar versus

citigroup

the Euro and Yen subside; and 3) a strengthening US economy could lead to a negative sector rotation, as the med tech industry is non-cyclical in nature.

On the contrary, shares of Guidant could fall below our target price should the company's ICD market share losses continue or should legal problems relating to the recent DOJ subpoena or the SEC investigation arise. These situations would likely cause the deal to break for a second time, which could also cause Guidant to fall below our target.

Boston Scientific (BSX– $25.05; 2H)

Valuation

Our price target on Boston Scientific remains $27. Our $27 target price is based off an average of three different valuations: 1) a 15x multiple off our forward 12 months (F12M ending 3Q:06) EPS forecast of $1.75; 2) a TEV/EBITDA target multiple of 10x; and 3) a 10-year DCF analysis.

A 15x P/E multiple represents a 30%-35% discount our CMTI F12M group multiple of 22x and is based on a forecast of minimal EPS growth from 2005-08 and the heightened risk that TAXUS share could fall below our Street low expectations. The CMTI is comprised of 17 large-cap medical devices companies, including companies such as Johnson & Johnson, Medtronic, and Alcon. The range of the CMTI F12M P/E multiples is from 15x to 33x.

Our TEV/EBITDA target multiple of 10x is also based on Boston trading at a 30%-35% discount to the current CMTI multiple of 17x. The comp group has changed ever so slightly since our last published note, pushing our multiple target for BSX to round down from 11x to 10x. This said, the difference in value is minimal. The TEV/EBITDA range for the CMTI is from 10x to 32x current enterprise value to projected 2005 EBITDA.

Boston Scientific Valuation Ratios

	Current	CMTI	Cardio Peers	S&P 500	Multiple Target	Target Price	Total Return
Price/F12M EPS	14x	23x	31x	19x	15x	$26.12	4%
TEV/EBITDA	10x	17x	23x		10x	$28.62	14%
Implied DCF Value	--					$26.31	5%
Derived Price Target						$27.01	8%
Dividend Yeild							0%
Expected Total Return							8%

Source: Citigroup Investment Research

Our DCF valuation of $27 per share is based on 10 years of projected free cash flow with a 1% terminal growth rate. For an equity risk premium we used 3.9%, our adjusted beta is 1.51 and our WACC is 8.9%.

Risks

We rate BSX shares High Risk. Investment risks particular to Boston Scientific include:

- **Reliance on a single product line.** The expected performance of the TAXUS stent in 2005 means that 40% of sales and 50% of EPS will come from a single product line. No other large-cap med tech company has this level of sales and EPS concentrated in one product line and recent data has led to questions about the safety profile of this stent.

citigroup

- **Patent risk surrounding the TAXUS stent.** Boston remains in litigation with JNJ over key stent patents in the US. Boston recently lost initial jury decisions on two JNJ patents (Palmaz and Gray), but won decisions on two of its own patents (Ding and Yang). These cases are unlikely to be resolved anytime soon, but could ultimately result in a large damage award or injunctive relief.
- **Competitive ASP pressure in the DES market in excess of our forecast.** We expect US DES ASPs to decline by 5% annually through 2008. Primary DES competitor JNJ is larger and better capitalized and has already been using price to win back DES market share in the US.

We would also highlight that BSX has recently announced its intentions to bid for Guidant. A culmination of this deal could adversely provide new risk to our BSX rating in either direction, as it could cause BSX share to fall due to possible dilution or could cause share to increase in value based on improved long-term prospects for BSX.

Our High Risk rating is primarily based on the company's significant reliance on a single product line combined with the outstanding legal issues noted above.

Investment risks relating to the medical supplies and technology ("med tech") industry include: 1) modest pricing pressure across most major product lines; 2) a reduction in sales and EPS benefit from FX as favorable Y/Y comparisons of the US dollar vs. the Euro and Yen subside in Q4; and 3) negative sector rotation if the US economy remains strong, as the med tech industry is non-cyclical in nature.

The above factors highlight some of the risks associated with investing in Boston Scientific's shares (for a more detailed list, please see the company's most recent 10-K filing). If any of the above-mentioned risk factors has a more negative impact on the company than we anticipate, the stock will likely have difficulty achieving our target price. Conversely, if any of these risk factors has less of an impact on the company's fundamentals, the stock could materially outperform our price target.

citigroup

ANALYST CERTIFICATION

APPENDIX A-1

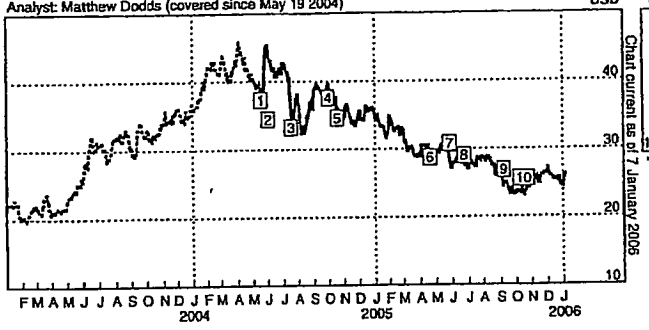
I, Matthew J. Dodds, research analyst and the author of this report, hereby certify that all of the views expressed in this research report accurately reflect my personal views about any and all of the subject issuer(s) or securities. I also certify that no part of my compensation was, is, or will be directly or indirectly related to the specific recommendation(s) or view(s) in this report.

IMPORTANT DISCLOSURES

Boston Scientific (BSX)

Ratings and Target Price History - Fundamental Research

Analyst: Matthew Dodds (covered since May 19 2004)



Covered
Not covered

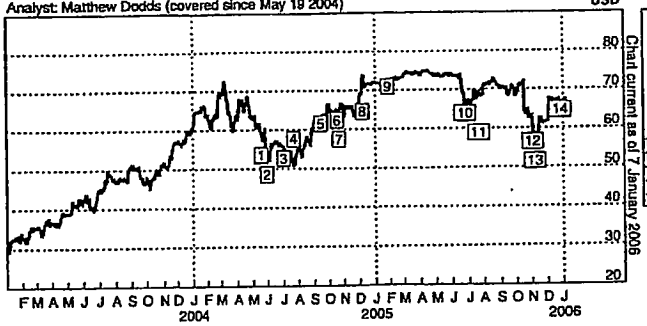
#	Date	Rating	Target Price	Closing Price
1:	18 May 04	*2H	*40.00	38.98
2:	2 Jun 04	2H	*46.00	44.70
3:	19 Jul 04	2H	*38.00	36.15
4:	30 Sep 04	2H	*40.00	39.73
5:	19 Oct 04	2H	*39.00	35.15
6:	20 Apr 05	2H	*34.00	28.75
7:	26 May 05	2H	*33.00	28.16
8:	23 Jun 05	2H	*31.00	27.81
9:	8 Sep 05	2H	*28.00	25.18
10:	16 Oct 05	2H	*27.00	23.57

*Indicates change.

Guidant Corporation (GDT)

Ratings and Target Price History - Fundamental Research

Analyst: Matthew Dodds (covered since May 18 2004)



Covered
Not covered

#	Date	Rating	Target Price	Closing Price
1:	18 May 04	*3H	*57.00	59.07
2:	28 May 04	3H	*53.00	54.34
3:	1 Jul 04	3H	*51.00	55.50
4:	22 Jul 04	*2H	51.00	50.55
5:	15 Sep 04	*3H	*54.00	63.54
6:	17 Oct 04	3H	*55.00	64.50
7:	21 Oct 04	3H	*56.00	63.67
8:	7 Dec 04	3H	*59.00	72.35
9:	27 Jan 05	*2H	*76.00	72.00
10:	24 Jun 05	2H	*70.00	63.90
11:	21 Jul 05	2H	*76.00	69.63
12:	2 Nov 05	*3H	*54.00	60.40
13:	7 Nov 05	3H	*50.00	57.52
14:	27 Dec 05	3H	*48.00	64.69

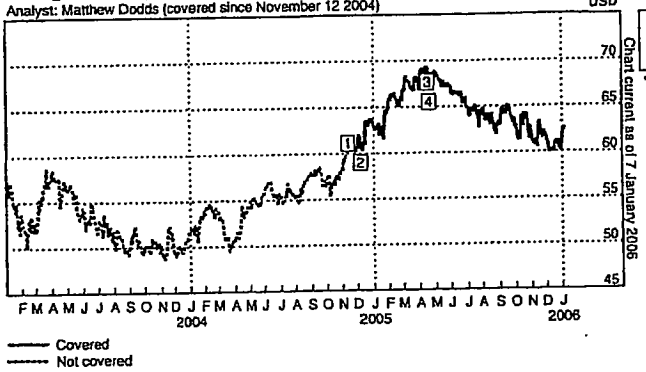
*Indicates change.

citigroup

Johnson & Johnson (JNJ)

Ratings and Target Price History - Fundamental Research

Analyst: Matthew Dodds (covered since November 12 2004)



#	Date	Rating	Target Price	Closing Price
1:	11 Nov 04	*1L	*71.00	60.60
2:	7 Dec 04	1L	*72.00	60.41
3:	18 Apr 05	1L	*76.00	69.04
4:	20 Apr 05	1L	*80.00	68.10

*Indicates change.

Customers of the Firm in the United States can receive independent, third-party research on the company or companies covered in this report, at no cost to them, where such research is available. Customers can access this independent research at http://www.smithbarney.com (for retail clients) or http://www.citigroupgeo.com (for institutional clients) or can call (866) 836-9542 to request a copy of this research.

A director of Citigroup Inc. serves as a director ofJohnson & Johnson.

Citigroup Global Markets Inc. and/or its affiliates has a significant financial interest in relation to Johnson & Johnson. (For an explanation of the determination of significant financial interest, please refer to the policy for managing conflicts of interest which can be found at www.citigroupgeo.com .)

Citigroup Global Markets Inc. and/or its affiliates has a significant financial interest in relation to Guidant Corporation. (For an explanation of the determination of significant financial interest, please refer to the policy for managing conflicts of interest which can be found at www.citigroupgeo.com .)

Citigroup Global Markets Inc. or its affiliates beneficially owns 1% or more of any class of common equity securities of Guidant Corporation. This position reflects information available as of the prior business day.

Citigroup Global Markets Inc. or an affiliate received compensation for products and services other than investment banking services from Boston Scientific, Guidant Corporation and Johnson & Johnson in the past 12 months.

Citigroup Global Markets Inc. currently has, or had within the past 12 months, the following company(ies) as clients, and the services provided were non-investment-banking, securities-related: Boston Scientific, Guidant Corporation and Johnson & Johnson.

Citigroup Global Markets Inc. currently has, or had within the past 12 months, the following company(ies) as clients, and the services provided were non-investment-banking, non-securities-related: Boston Scientific, Guidant Corporation and Johnson & Johnson.

Analysts' compensation is determined based upon activities and services intended to benefit the investor clients of Citigroup Global Markets Inc. and its affiliates ("the Firm"). Like all Firm employees, analysts receive compensation that is impacted by overall firm profitability, which includes revenues from, among other business units, the Private Client Division, Institutional Equities, and Investment Banking.

The Firm is a market maker in the publicly traded equity securities of Boston Scientific, Guidant Corporation and Johnson & Johnson.

Citigroup Investment Research Ratings Distribution

Data current as of 31 December 2005	Buy	Hold	Sell
Citigroup Investment Research Global Fundamental Coverage (2784)	42%	41%	17%
% of companies in each rating category that are investment banking clients	47%	48%	37%
Medical Supplies & Technology – North America (9)	44%	33%	22%
% of companies in each rating category that are investment banking clients	50%	33%	50%

Guide to Fundamental Research Investment Ratings:

Citigroup Investment Research's stock recommendations include a risk rating and an investment rating.

Risk ratings, which take into account both price volatility and fundamental criteria, are: Low (L), Medium (M), High (H), and Speculative (S).

Investment ratings are a function of Citigroup Investment Research's expectation of total return (forecast price appreciation and dividend yield within the next 12 months) and risk rating.

For securities in developed markets (US, UK, Europe, Japan, and Australia/New Zealand), investment ratings are: Buy (1) (expected total return of 10% or more for Low-Risk stocks, 15% or more for Medium-Risk stocks, 20% or more for High-Risk stocks, and 35% or more for Speculative stocks); Hold (2) (0%-10% for Low-Risk stocks, 0%-15% for Medium-Risk stocks, 0%-20% for High-Risk stocks, and 0%-35% for Speculative stocks); and Sell (3) (negative total return).

Investment ratings are determined by the ranges described above at the time of initiation of coverage, a change in investment and/or risk rating, or a change in target price (subject to limited management discretion). At other times, the expected total returns may fall outside of these ranges because of market price movements and/or other short-term volatility or trading patterns. Such interim deviations from

citigroup

specified ranges will be permitted but will become subject to review by Research Management. Your decision to buy or sell a security should be based upon your personal investment objectives and should be made only after evaluating the stock's expected performance and risk.

Between September 9, 2002, and September 12, 2003, Citigroup Investment Research's stock ratings were based upon expected performance over the following 12 to 18 months relative to the analyst's industry coverage universe at such time. An Outperform (1) rating indicated that we expected the stock to outperform the analyst's industry coverage universe over the coming 12-18 months. An In-line (2) rating indicated that we expected the stock to perform approximately in line with the analyst's coverage universe. An Underperform (3) rating indicated that we expected the stock to underperform the analyst's coverage universe. In emerging markets, the same ratings classifications were used, but the stocks were rated based upon expected performance relative to the primary market index in the region or country. Our complementary Risk rating system -- Low (L), Medium (M), High (H), and Speculative (S) -- took into account predictability of financial results and stock price volatility. Risk ratings for Asia Pacific were determined by a quantitative screen which classified stocks into the same four risk categories. In the major markets, our Industry rating system -- Overweight, Marketweight, and Underweight -- took into account each analyst's evaluation of their industry coverage as compared to the primary market index in their region over the following 12 to 18 months.

OTHER DISCLOSURES

Within the past 5 years, Citigroup Global Markets Inc. or its affiliates has acted as manager or co manager of a public offering of fixed income securities of Boston Scientific and Johnson & Johnson.

Citigroup Global Markets Inc. or its affiliates beneficially owns 2% or more of any class of common equity securities of Guidant Corporation.

Citigroup Global Markets Inc. or its affiliates holds a long position in any class of common equity securities of Guidant Corporation.

For securities recommended in the Product in which the Firm is not a market maker, the Firm is a liquidity provider in the issuers' financial instruments and may act as principal in connection with such transactions. The Firm is a regular issuer of traded financial instruments linked to securities that may have been recommended in the Product. The Firm regularly trades in the securities of the subject company(ies) discussed in the Product. The Firm may engage in securities transactions in a manner inconsistent with the Product and, with respect to securities covered by the Product, will buy or sell from customers on a principal basis.

Securities recommended, offered, or sold by the Firm: (i) are not insured by the Federal Deposit Insurance Corporation; (ii) are not deposits or other obligations of any insured depository institution (including Citibank); and (iii) are subject to investment risks, including the possible loss of the principal amount invested. Although information has been obtained from and is based upon sources that the Firm believes to be reliable, we do not guarantee its accuracy and it may be incomplete and condensed. Note, however, that the Firm has taken all reasonable steps to determine the accuracy and completeness of the disclosures made in the Important Disclosures section of the Product. In producing Products, members of the Firm's research department may have received assistance from the subject company(ies) referred to in the Product. Any such assistance may have included access to sites owned, leased or otherwise operated or controlled by the issuers and meetings with management, employees or other parties associated with the subject company(ies). Firm policy prohibits research analysts from sending draft research to subject companies. However, it should be presumed that the author of the Product has had discussions with the subject company to ensure factual accuracy prior to publication. All opinions, projections and estimates constitute the judgment of the author as of the date of the Product and are subject to change without notice. Prices and availability of financial instruments also are subject to change without notice. Although Citigroup Investment Research does not set a predetermined frequency for publication, if the Product is a fundamental research report, it is the intention of Citigroup Investment Research to provide research coverage of the/those issuer(s) mentioned therein, including in response to news affecting this issuer, subject to applicable quiet periods and capacity constraints. The Product is for informational purposes only and is not intended as an offer or solicitation for the purchase or sale of a security. Any decision to purchase securities mentioned in the Product must take into account existing public information on such security or any registered prospectus.

Investing in non-U.S. securities, including ADRs, may entail certain risks. The securities of non-U.S. issuers may not be registered with, nor be subject to the reporting requirements of the U.S. Securities and Exchange Commission. There may be limited information available on foreign securities. Foreign companies are generally not subject to uniform audit and reporting standards, practices and requirements comparable to those in the U.S. Securities of some foreign companies may be less liquid and their prices more volatile than securities of comparable U.S. companies. In addition, exchange rate movements may have an adverse effect on the value of an investment in a foreign stock and its corresponding dividend payment for U.S. investors. Net dividends to ADR investors are estimated, using withholding tax rates conventions, deemed accurate, but investors are urged to consult their tax advisor for exact dividend computations. Investors who have received the Product from the Firm may be prohibited in certain states or other jurisdictions from purchasing securities mentioned in the Product from the Firm. Please ask your Financial Consultant for additional details. Citigroup Global Markets Inc. takes responsibility for the Product in the United States. Any orders by non-US investors resulting from the information contained in the Product may be placed only through Citigroup Global Markets Inc.

The Citigroup legal entity that takes responsibility for the production of the Product is the legal entity which the first named author is employed by. The Product is made available in Australia to wholesale clients through Citigroup Global Markets Australia Pty Ltd. (ABN 64 003 114 832 and AFSL No. 240992) and to retail clients through Citigroup Wealth Advisors Pty Ltd. (ABN 19 009 145 555 and AFSL No. 240813), Participants of the ASX Group and regulated by the Australian Securities & Investments Commission. Citigroup Centre, 2 Park Street, Sydney, NSW 2000. If the Product is being made available in certain provinces of Canada by Citigroup Global Markets (Canada) Inc. ("CGM Canada"), CGM Canada has approved the Product. Citigroup Place, 123 Front Street West, Suite 1100, Toronto, Ontario M5J 2M3. The Product may not be distributed to private clients in Germany. The Product is distributed in Germany by Citigroup Global Markets Deutschland AG & Co. KGaA, which is regulated by Bundesanstalt fuer Finanzdienstleistungsaufsicht (BaFin). Frankfurt am Main, Reuterweg 16, 60323 Frankfurt am Main. If the Product is made available in Hong Kong by, or on behalf of, Citigroup Global Markets Asia Ltd., it is attributable to Citigroup Global Markets Asia Ltd., Citibank Tower, Citibank Plaza, 3 Garden Road, Hong Kong. Citigroup Global Markets Asia Ltd. is regulated by Hong Kong Securities and Futures Commission. If the Product is made available in Hong Kong by The Citigroup Private Bank to its clients, it is attributable to Citibank N.A., Citibank Tower, Citibank Plaza, 3 Garden Road, Hong Kong. The Citigroup Private Bank and Citibank N.A. is regulated by the Hong Kong Monetary Authority. The Product is made

citigroup

available in India by Citigroup Global Markets India Private Limited, which is regulated by Securities and Exchange Board of India. Bakhtawar, Nariman Point, Mumbai 400-021. If the Product was prepared by Citigroup Investment Research and distributed in Japan by Nikko Citigroup Ltd., it is being so distributed under license. Nikko Citigroup Limited is regulated by Financial Services Agency, Securities and Exchange Surveillance Commission, Japan Securities Dealers Association, Tokyo Stock Exchange and Osaka Securities Exchange. Akasaka Park Building, 2-20, Akasaka 5-chome, Minato-ku, Tokyo 107-6122. The Product is made available in Korea by Citigroup Global Markets Korea Securities Ltd., which is regulated by Financial Supervisory Commission and the Financial Supervisory Service. Hungkuk Life Insurance Building, 226 Shinmunno 1-GA, Jongno-Gu, Seoul, 110-061. The Product is made available in Malaysia by Citigroup Global Markets Malaysia Sdn Bhd, which is regulated by Malaysia Securities Commission. Menara Citibank, 165 Jalan Ampang, Kuala Lumpur, 50450. The Product is made available in Mexico by Acciones y Valores Banamex, S.A. De C. V., Casa de Bolsa, which is regulated by Comision Nacional Bancaria y de Valores. Reforma 398, Col. Juarez, 06600 Mexico, D.F. In New Zealand the Product is made available through Citigroup Global Markets New Zealand Ltd., a Participant of the New Zealand Exchange Limited and regulated by the New Zealand Securities Commission. Level 19, Mobile on the Park, 157 lambton Quay, Wellington. The Product is made available in Poland by Dom Maklerski Banku Handlowego SA an indirect subsidiary of Citigroup Inc., which is regulated by Komisja Papierów Wartosciowych i Gield. Bank Handlowy w Warszawie S.A. ul. Senatorska 16, 00-923 Warszawa. The Product is made available in the Russian Federation through ZAO Citibank, which is licensed to carry out banking activities in the Russian Federation in accordance with the general banking license issued by the Central Bank of the Russian Federation and brokerage activities in accordance with the license issued by the Federal Service for Financial Markets. Neither the Product nor any information contained in the Product shall be considered as advertising the securities mentioned in this report within the territory of the Russian Federation or outside the Russian Federation. The Product does not constitute an appraisal within the meaning of the Federal Law of the Russian Federation of 29 July 1998 No. 135-FZ (as amended) On Appraisal Activities in the Russian Federation. 8-10 Gasheka Street, 125047 Moscow. The Product is made available in Singapore through Citigroup Global Markets Singapore Pte. Ltd., a Capital Markets Services Licence holder, and regulated by Monetary Authority of Singapore. 1 Temasek Avenue, #39-02 Millenia Tower, Singapore 039192. Citigroup Global Markets (Pty) Ltd. is incorporated in the Republic of South Africa (company registration number 2000/025866/07) and its registered office is at 145 West Street, Sandton, 2196, Saxonwold. Citigroup Global Markets (Pty) Ltd. is regulated by JSE Securities Exchange South Africa, South African Reserve Bank and the Financial Services Board. The investments and services contained herein are not available to private customers in South Africa. The Product is made available in Taiwan through Citigroup Global Markets Inc. (Taipei Branch), which is regulated by Securities & Futures Bureau. No portion of the report may be reproduced or quoted in Taiwan by the press or any other person. No. 8 Manhattan Building, Hsin Yi Road, Section 5, Taipei 100, Taiwan. The Product is made available in United Kingdom by Citigroup Global Markets Limited, which is regulated by Financial Services Authority. This material may relate to investments or services of a person outside of the UK or to other matters which are not regulated by the FSA and further details as to where this may be the case are available upon request in respect of this material. Citigroup Centre, Canada Square, Canary Wharf, London, E14 5LB. The Product is made available in United States by Citigroup Global Markets Inc, which is regulated by NASD, NYSE and the US Securities and Exchange Commission. 388 Greenwich Street, New York, NY 10013. Unless specified to the contrary, within EU Member States, the Product is made available by Citigroup Global Markets Limited, which is regulated by Financial Services Authority. Many European regulators require that a firm must establish, implement and make available a policy for managing conflicts of interest arising as a result of publication or distribution of investment research. The policy applicable to Citigroup Investment Research's Products can be found at www.citigroupgeo.com. Compensation of equity research analysts is determined by equity research management and Citigroup's senior management and is not linked to specific transactions or recommendations. The Product may have been distributed simultaneously, in multiple formats, to the Firm's worldwide institutional and retail customers. The Product is not to be construed as providing investment services in any jurisdiction where the provision of such services would be illegal. Subject to the nature and contents of the Product, the investments described therein are subject to fluctuations in price and/or value and investors may get back less than originally invested. Certain high-volatility investments can be subject to sudden and large falls in value that could equal or exceed the amount invested. Certain investments contained in the Product may have tax implications for private customers whereby levels and basis of taxation may be subject to change. If in doubt, investors should seek advice from a tax adviser. Advice in the Product has been prepared without taking account of the objectives, financial situation or needs of any particular investor. Accordingly, investors should, before acting on the advice, consider the appropriateness of the advice, having regard to their objectives, financial situation and needs.

ADDITIONAL INFORMATION IS AVAILABLE UPON REQUEST

Exhibit J

citigroup

See page 6 for Analyst Certification and Important Disclosures

Multi-Company Note

Medical Supplies & Technology

Deconstructing Xience

March 23, 2006

Matthew J Dodds
+1-212-816-6928
matthew.dodds@citigroup.com

United States

SUMMARY

- Our work on the intellectual property (IP) challenges facing GDT's Xience stent suggests: 1) the BSX/GDT deal may not close on time and 2) ABT's purchase price for GDT's Vascular business looks excessive.
- We uncoupled the key components of Guidant's Xience drug-eluting stent and found potential IP issues on each piece.
- GDT's Vision stent appears to have a difficult roadblock against a stent patent held by Evysio that was recently licensed by MDT. This patent was recently found valid and novel by the EPO and has recently been asserted in the US.
- Everolimus will likely face two IP challenges from JNJ as both its Falotico and Wright patents claim the use of a limus analogue on a stent.
- GDT's polymer is also likely to face issues as several patents in this arena were issued before GDT even developed this polymer.

SUMMARY VALUATION AND RECOMMENDATION DATA

		Expected Returns								Earnings Per Share	
Company (Ticker)	Price	Price	Div.	Total		Rating	Div.(E)	Target	LTGR	Current Yr	Next Yr
Abbott Laboratories-	$44.10	(13.8%)	2.4%	(11.4%)	Curr	3M	$1.07	$38.00	7%	$2.52E	$2.65E
(ABT)					Prev	3M	$1.07	$38.00	7%	$2.52E	$2.65E
Boston Scientific-	$23.47	(2.0%)	0.0%	(2.0%)	Curr	2S	$0.00	$23.00	7%	$1.56E	$1.61E
(BSX)					Prev	2S	$0.00	$23.00	7%	$1.56E	$1.61E
Conor Medsystems-	$28.73	18.3%	0.0%	18.3%	Curr	1S	$0.00	$34.00	NA	($0.92)E	$0.33E
(CONR)					Prev	1S	$0.00	$34.00	NA	($0.92)E	$0.33E
Guidant Corporation-	$78.76	(46.7%)	0.5%	(46.2%)	Curr	3S	$0.40	$42.00	15%	$1.81E	$1.30E
(GDT)					Prev	3S	$0.40	$42.00	15%	$1.81E	$1.30E
Johnson & Johnson-	$61.00	31.1%	2.1%	33.3%	Curr	1L	$1.29	$80.00	11%	$3.49E	$3.84E
(JNJ)					Prev	1L	$1.29	$80.00	11%	$3.49E	$3.84E
Medtronic (MDT)	$53.83	26.3%	0.6%	27.0%	Curr	1L	$0.34	$68.00	17%	$2.22E	$2.54E
					Prev	1L	$0.34	$68.00	17%	$2.22E	$2.54E

OPINION

Deconstructing Xience....We know more about the IP than the efficacy

We have spent the past few weeks reviewing the intellectual propery (IP) position of Guidant's highly-touted Xience drug-eluting stent. Our work included discussions with several companies in the drug-eluting stent space and a review by a patent expert. This work suggests the Xience stent faces several hurdles on the intellectual property front

citigroup

that essentially cover the system through all of its primary components. While not a complete review, our analysis strongly suggests Abbott is paying a very hefty price given the IP risk and it is likely the FTC review of this IP landscape makes an early April close of the Boston/Guidant merger appear unlikely.

The stent (Vision)

Guidant's Vision stent is made of cobalt-chromium and is viewed as one of the premier bare metal stents along with Medtronic's Driver. The Vision has faced little patent opposition to date with the exception of a recent (February 10) negative decision on one patent by privately-held Medinol in the Southern district of New York. This trial is still proceeding as Guidant has challenged the patent's validity.

In Guidant's recent 10-K, another lawsuit was noted that could end up being an even bigger hurdle to Vision, especially in Europe. The case – filed in the Northern District of California on 2/16 – claims infringement by several of Guidant's balloon catheters and the Vision stent. The plaintiff in the case is Medtronic and privately-held Evysio Medical Devices, based in Vancouver.

The most interesting component of this lawsuit is the patent being asserted against the Vision – 6'858'037. This patent is owned by Evysio, but was recently licensed exclusively by Medtronic. This patent has already shown its strength in one European court and our patent work suggests the US claims are very similar.

In France, Evysio filed suit against Guidant's Vision stent soon after it was launched in 2003 seeking a preliminary injunction. At the core of this case was Evysio's patent EPO888093, which corresponds to US patent '037. On December 17, 2004, Evysio's request for a permanent injunction was not granted, but our review of the decision shows the Paris Court's decision heavily favored Evysio. While an injunction was not granted, most of Guidant's claims to dismiss the case (i.e., scope of the patent, priority date, novelty) were dismissed. In addition, the court determined that the "action on the merits seems to be serious" and Guidant was forced to post an 800,000 EUR bond pending a final decision on the case.

Since Guidant challenged the validity of the '093 patent, the case was stayed pending an Opposition Proceeding at the European Patent Office (EPO). Earlier this month, the EPO upheld the '093 patent and now the case in France can proceed. While this trial isn't likely to start until later in the year, the initial findings of the Paris court and the EPO decision put high odds on the Vision being found to infringe on the '093 patent.

Given that France is just one country in the European market (albeit the largest one) and the case may not have a final appellate decision for a couple of years, this case doesn't seem too troubling at first blush. Digging a bit deeper, we believe this case is a foreboding sign for Vision on two fronts.

First, with the favorable EPO decision and Medtronic's deep pockets, we expect Evysio and Medtronic to go after the Vision stent in several countries, including Ireland, where it is manufactured. If Vision is found to infringe in Ireland, it could lead to a lack of supply for this product in Europe.

In the US, we have compared the European '093 patent with the '037 US version and then templated the claims against the design of the Vision stent.

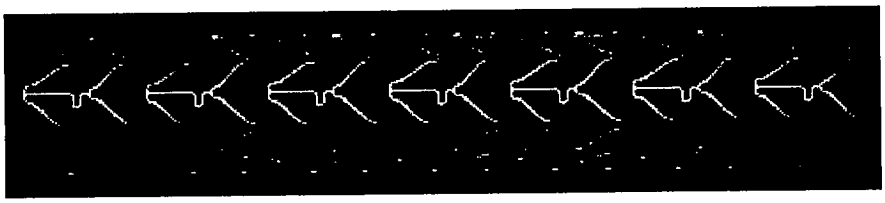
Claim 1 of the '037 patent is directed to:

An unexpanded stent comprising:

citigroup

- a tubular wall having a series of undulating circumferential portions, each circumferential portion comprising alternating peaks and valleys;
- the tubular wall also having a plurality of longitudinal portions connecting said series of undulating circumferential portions to form a porous, cylindrical surface;
- a longitudinal portion connecting a peak in a first circumferential portion with a valley in a second circumferential portion adjacent to the first circumferential portion; and
- each longitudinal portion having a flexure member, said flexure member, in two dimensions, being non-sinusoidal and arcuate, each flexure member being connected to an adjacent circumferential portion with a straight strut portion which is disposed parallel to a longitudinal axis of the stent.

The Guidant Multi-link stent is reproduced below:



Based upon our legal expert's comparison of the claim language of claim 1 to the picture of the Guidant Multi-link stent, the claim language appears to literally read on the Guidant Multi-link stent. The novelty of claim 1 appears to reside in the "flexure member" which is described as "non-sinusoidal and arcuate." In the Guidant Multi-link is the U-shaped member appears to correspond to the "flexure member" of the '037 patent. We have also looked at the file history of the '037 patent, and it appears that the language describing the "flexure member" was amended during prosecution of the patent.

The French decision describes claim 1 of the '093 patent, and the language of the U.S. and EPO patents are different, but claim 1 of the EPO patent also appears to be directed to the "flexure member." The EPO patent has also been amended to include a limitation directed to "laser cutting."

If we assume the '037 patent is valid (based on the favorable EPO review), the burden of proof will fall on Guidant to build a case of non-infringement. Our patent expert believes this will have to be based on prior art, which is a difficult hurdle, and suggests a 60-70% chance of success for the plaintiff.

The drug (everolimus)

Guidant obtained exclusive rights to using the drug everolimus on a stent from Novartis back in 2002. Unfortunately, obtaining rights to use the drug on a stent and holding the IP to use the drug on a stent are two entirely different things.

Over the past couple of months, potential blocking IP on using a derivative of Rapamycin, the drug JNJ uses on its Cypher stent, has surfaced. This IP originally showed up as part of JNJ's agreement with Abbott in order to receive FTC approval for the acquisition of Guidant While JNJ originally offered Abbott what was believed to be the key to a deal – access to rapid exchange delivery system patents – Abbott apparently lobbied the FDA for two other patent portfolios owned by JNJ. These patents, broadly known as Falotico (6'776'796) and Wright (6'585'764) – were apparently deemed to be vital to the use of a limus "analogue" on a stent and both everolimus and zotarolimus (the drug used in ZoMaxx) fall under this definition of an analogue. JNJ ended up being required to license both patents to Abbott for

citigroup

its ZoMaxx stent program in order to satisfy the FTC, but the deal ended up dying along with JNJ's acquisition of Guidant once Boston Scientific entered the picture.

What is interesting about this change is that Abbott is now acquiring Guidant's Xience platform alongside its ZoMaxx platform yet neither product will have access to the '796 or '764 patents. Hence, both products could be found to infringe these patents. This puts the FTC in an interesting spot as the agency was compelled to make sure Abbott received access to these patents in its approval of the JNJ/Guidant combination and will now have to be comfortable that Abbott will still be considered a viable player without access.

Of the two patents, the '796 appears to be particularly damaging as it was filed in 2001 and now has over 27 follow on patents pending with the PTO.

The polymer

Guidant finally unveiled the composition of the polymer on the Xience stent during a presentation at the ACC last week. While the name of the polymer was not provided, we did see background information on the composition – acrylic and flourinated polymers. We looked into the IP around this polymer composition and found a handful of patents granted to JNJ's polymer supplier Surmodix and a patent on flourinated polymers by Medtronic (Nolting, 6'488'701) that was filed all the way back in 1998 and issued in December 2002. We also believe JNJ's Ethicon division may have some patents around both acrylic and flourinated polymers.

It should also be noted that Guidant is likely to have trouble moving from its current durable polymer to a bioaborbable one. As we noted in our March 14 note (*ACC 2006: DES Behind the Scenes*) concerns about late thrombosis with durable polymers appears to be driving the industry toward bioerodable polymers where Conor currently holds the lead.

While we do not believe Guidant has any version of Xience with a bioerodable polymer in the works, any work in this area could be subject to IP from its jilted partner Biosensors. Biosensors has a patent – 6'939'376 – that was just issued in September 2005 that covers immuno-suppressive drugs, including everolimus, on a stent with a biodegradable polymer. While we believe Guidant may technically have rights to this patent since its partnership with Biosensors has not been officially severed, it does appear well on its way since Biosensors Occam subsidiary sued Guidant in California on January 20 under the allegation that Guidant breached its contractual obligations.

What can happen from here

Near term, there are two events to look out for relating to these patents. First, we believe JNJ's '796 and '764 patents will need to be strongly considered by the FTC, which is likely to make Boston's plan to close the Guidant deal by April 3 unrealistic. Second, we would not be surprised to see Medtronic and Evysio file suit in Ireland shortly, which could put the EU launch of the Xience at risk.

Longer-term, the IP issues looming could be a major problem for Abbott given the amount of money that it is paying for Xience and the Street's bullish stance on Abbott's interventional cardiology prospects post the Guidant deal. Based on our analysis, Abbott would have been better off sticking with JNJ and not helping Boston win the bidding war since it would have had broader IP access and paid a much lower price. For Abbott to take this risk, we can only assume the company's expectation for either the efficacy or approval timing of its ZoMaxx platform is less optimistic than the Street's projections.

citigroup

For Medtronic, the licensing of the Evysio patents could prove a key chip to barter for access to rapid exchange and/or the Lau patents.

QUARTERLY ESTIMATES PER SHARE DATA

		Current Year		Next Year		Next Year + 1	
Ticker	Period	Current	Previous	Current	Previous	Current	Previous
ABT	1Q	$0.60E	$0.60E	NA	NA	NA	NA
(FYE Dec)	2Q	$0.61E	$0.61E	NA	NA	NA	NA
	3Q	$0.61E	$0.61E	NA	NA	NA	NA
	4Q	$0.70E	$0.70E	NA	NA	NA	NA
	Year	$2.52E	$2.52E	$2.65E	$2.65E	$2.78E	$2.78E
BSX	1Q	$0.42E	$0.42E	NA	NA	NA	NA
(FYE Dec)	2Q	$0.41E	$0.41E	NA	NA	NA	NA
	3Q	$0.37E	$0.37E	NA	NA	NA	NA
	4Q	$0.36E	$0.36E	NA	NA	NA	NA
	Year	$1.56E	$1.56E	$1.61E	$1.61E	$1.60E	$1.60E
CONR	1Q	($0.35)E	($0.35)E	NA	NA	NA	NA
(FYE Dec)	2Q	($0.21)E	($0.21)E	NA	NA	NA	NA
	3Q	($0.20)E	($0.20)E	NA	NA	NA	NA
	4Q	($0.16)E	($0.16)E	NA	NA	NA	NA
	Year	($0.92)E	($0.92)E	$0.33E	$0.33E	$2.15E	$2.15E
GDT	1Q	$0.65A	$0.65A	$0.30E	$0.30E	NA	NA
(FYE Dec)	2Q	$0.63A	$0.63A	$0.38E	$0.38E	NA	NA
	3Q	$0.28A	$0.28A	$0.33E	$0.33E	NA	NA
	4Q	$0.25A	$0.25A	$0.29E	$0.29E	NA	NA
	Year	$1.81E	$1.81E	$1.30E	$1.30E	$1.93E	$1.93E
JNJ	1Q	$0.97A	$0.97A	$1.04E	$1.04E	NA	NA
(FYE Dec)	2Q	$0.93A	$0.93A	$1.03E	$1.03E	NA	NA
	3Q	$0.87A	$0.87A	$1.00E	$1.00E	NA	NA
	4Q	$0.73A	$0.73A	$0.77E	$0.77E	NA	NA
	Year	$3.49E	$3.49E	$3.84E	$3.84E	$4.21E	$4.21E
MDT	1Q	$0.50A	$0.50A	NA	NA	NA	NA
(FYE Apr)	2Q	$0.54A	$0.54A	NA	NA	NA	NA
	3Q	$0.55E	$0.55E	NA	NA	NA	NA
	4Q	$0.63E	$0.63E	NA	NA	NA	NA
	Year	$2.22E	$2.22E	$2.54E	$2.54E	$2.94E	$2.94E

citigroup

ANALYST CERTIFICATION

APPENDIX A-1

I, Matthew Dodds, research analyst and the author of this report, hereby certify that all of the views expressed in this research report accurately reflect my personal views about any and all of the subject issuer(s) or securities. I also certify that no part of my compensation was, is, or will be directly or indirectly related to the specific recommendation(s) or view(s) in this report.

IMPORTANT DISCLOSURES

Analysts' compensation is determined based upon activities and services intended to benefit the investor clients of Citigroup Global Markets Inc. and its affiliates ("the Firm"). Like all Firm employees, analysts receive compensation that is impacted by overall firm profitability, which includes revenues from, among other business units, the Private Client Division, Institutional Equities, and Investment Banking.

Citigroup Investment Research Ratings Distribution

Data current as of 31 December 2005	**Buy**	**Hold**	**Sell**
Citigroup Investment Research Global Fundamental Coverage (2784)	42%	41%	17%
% of companies in each rating category that are investment banking clients	47%	48%	37%

Guide to Fundamental Research Investment Ratings:
Citigroup Investment Research's stock recommendations include a risk rating and an investment rating.
Risk ratings, which take into account both price volatility and fundamental criteria, are: Low (L), Medium (M), High (H), and Speculative (S).
Investment ratings are a function of Citigroup Investment Research's expectation of total return (forecast price appreciation and dividend yield within the next 12 months) and risk rating.
For securities in developed markets (US, UK, Europe, Japan, and Australia/New Zealand), investment ratings are: Buy (1) (expected total return of 10% or more for Low-Risk stocks, 15% or more for Medium-Risk stocks, 20% or more for High-Risk stocks, and 35% or more for Speculative stocks); Hold (2) (0%-10% for Low-Risk stocks, 0%-15% for Medium-Risk stocks, 0%-20% for High-Risk stocks, and 0%-35% for Speculative stocks); and Sell (3) (negative total return).
For securities in emerging markets (Asia Pacific, Emerging Europe/Middle East/Africa, and Latin America), investment ratings are: Buy (1) (expected total return of 15% or more for Low-Risk stocks, 20% or more for Medium-Risk stocks, 30% or more for High-Risk stocks, and 40% or more for Speculative stocks); Hold (2) (5%-15% for Low-Risk stocks, 10%-20% for Medium-Risk stocks, 15%-30% for High-Risk stocks, and 20%-40% for Speculative stocks); and Sell (3) (5% or less for Low-Risk stocks, 10% or less for Medium-Risk stocks, 15% or less for High-Risk stocks, and 20% or less for Speculative stocks).
Investment ratings are determined by the ranges described above at the time of initiation of coverage, a change in investment and/or risk rating, or a change in target price (subject to limited management discretion). At other times, the expected total returns may fall outside of these ranges because of market price movements and/or other short-term volatility or trading patterns. Such interim deviations from specified ranges will be permitted but will become subject to review by Research Management. Your decision to buy or sell a security should be based upon your personal investment objectives and should be made only after evaluating the stock's expected performance and risk.

OTHER DISCLOSURES

For securities recommended in the Product in which the Firm is not a market maker, the Firm is a liquidity provider in the issuers' financial instruments and may act as principal in connection with such transactions. The Firm is a regular issuer of traded financial instruments linked to securities that may have been recommended in the Product. The Firm regularly trades in the securities of the subject company(ies) discussed in the Product. The Firm may engage in securities transactions in a manner inconsistent with the Product and, with respect to securities covered by the Product, will buy or sell from customers on a principal basis.

Securities recommended, offered, or sold by the Firm: (i) are not insured by the Federal Deposit Insurance Corporation; (ii) are not deposits or other obligations of any insured depository institution (including Citibank); and (iii) are subject to investment risks, including the possible loss of the principal amount invested. Although information has been obtained from and is based upon sources that the Firm believes to be reliable, we do not guarantee its accuracy and it may be incomplete and condensed. Note, however, that the Firm has taken all reasonable steps to determine the accuracy and completeness of the disclosures made in the Important Disclosures section of the Product. In producing Products, members of the Firm's research department may have received assistance from the subject company(ies) referred to in the Product. Any such assistance may have included access to sites owned, leased or otherwise operated or controlled by the issuers and meetings with management, employees or other parties associated with the subject company(ies). Firm policy prohibits research analysts from sending draft research to subject companies. However, it should be presumed that the author of the Product has had discussions with the subject company to ensure factual accuracy prior to publication. All opinions, projections and estimates constitute the judgment of the author as of the date of the Product and are subject to change without notice. Prices and availability of financial instruments also are subject to change without notice. Although Citigroup Investment Research does not set a predetermined frequency for publication, if the Product is a fundamental research report, it is the intention of Citigroup Investment Research to provide research coverage of the/those issuer(s) mentioned therein, including in response to news affecting this issuer, subject to applicable quiet periods and capacity constraints. The Product is for informational purposes only and is not intended as an offer or solicitation for the purchase or sale of a security. Any decision to purchase securities mentioned in the Product must take into account existing public information on such security or any registered prospectus.

Investing in non-U.S. securities, including ADRs, may entail certain risks. The securities of non-U.S. issuers may not be registered with, nor be subject to the reporting requirements of the U.S. Securities and Exchange Commission. There may be limited information available on foreign securities. Foreign companies are generally not subject to uniform audit and reporting standards, practices and requirements comparable to those in the U.S. Securities of some foreign companies may be less liquid and their prices more volatile than securities of comparable U.S. companies. In addition, exchange rate movements may have an adverse effect on the value of an investment in a foreign stock and its corresponding dividend payment for U.S. investors. Net dividends to ADR investors are estimated, using withholding tax rates conventions, deemed accurate, but investors are urged to consult their tax advisor for exact dividend computations. Investors who have received the Product from the Firm may be prohibited in certain states or other jurisdictions from

citigroup

purchasing securities mentioned in the Product from the Firm. Please ask your Financial Consultant for additional details. Citigroup Global Markets Inc. takes responsibility for the Product in the United States. Any orders by non-US investors resulting from the information contained in the Product may be placed only through Citigroup Global Markets Inc.

The Citigroup legal entity that takes responsibility for the production of the Product is the legal entity which the first named author is employed by. The Product is made available in Australia to wholesale clients through Citigroup Global Markets Australia Pty Ltd. (ABN 64 003 114 832 and AFSL No. 240992) and to retail clients through Citigroup Wealth Advisors Pty Ltd. (ABN 19 009 145 555 and AFSL No. 240813), Participants of the ASX Group and regulated by the Australian Securities & Investments Commission. Citigroup Centre, 2 Park Street, Sydney, NSW 2000. If the Product is being made available in certain provinces of Canada by Citigroup Global Markets (Canada) Inc. ("CGM Canada"), CGM Canada has approved the Product. Citigroup Place, 123 Front Street West, Suite 1100, Toronto, Ontario M5J 2M3. The Product may not be distributed to private clients in Germany. The Product is distributed in Germany by Citigroup Global Markets Deutschland AG & Co. KGaA, which is regulated by Bundesanstalt fuer Finanzdienstleistungsaufsicht (BaFin). Frankfurt am Main, Reuterweg 16, 60323 Frankfurt am Main. If the Product is made available in Hong Kong by, or on behalf of, Citigroup Global Markets Asia Ltd., it is attributable to Citigroup Global Markets Asia Ltd., Citibank Tower, Citibank Plaza, 3 Garden Road, Hong Kong. Citigroup Global Markets Asia Ltd. is regulated by Hong Kong Securities and Futures Commission. If the Product is made available in Hong Kong by The Citigroup Private Bank to its clients, it is attributable to Citibank N.A., Citibank Tower, Citibank Plaza, 3 Garden Road, Hong Kong. The Citigroup Private Bank and Citibank N.A. is regulated by the Hong Kong Monetary Authority. The Product is made available in India by Citigroup Global Markets India Private Limited, which is regulated by Securities and Exchange Board of India. Bakhtawar, Nariman Point, Mumbai 400-021. If the Product was prepared by Citigroup Investment Research and distributed in Japan by Nikko Citigroup Ltd., it is being so distributed under license. Nikko Citigroup Limited is regulated by Financial Services Agency, Securities and Exchange Surveillance Commission, Japan Securities Dealers Association, Tokyo Stock Exchange and Osaka Securities Exchange. Akasaka Park Building, 2-20, Akasaka 5-chome, Minato-ku, Tokyo 107-6122. The Product is made available in Korea by Citigroup Global Markets Korea Securities Ltd., which is regulated by Financial Supervisory Commission and the Financial Supervisory Service. Hungkuk Life Insurance Building, 226 Shinmunno 1-GA, Jongno-Gu, Seoul, 110-061. The Product is made available in Malaysia by Citigroup Global Markets Malaysia Sdn Bhd, which is regulated by Malaysia Securities Commission. Menara Citibank, 165 Jalan Ampang, Kuala Lumpur, 50450. The Product is made available in Mexico by Acciones y Valores Banamex, S.A. De C. V., Casa de Bolsa, which is regulated by Comision Nacional Bancaria y de Valores. Reforma 398, Col. Juarez, 06600 Mexico, D.F. In New Zealand the Product is made available through Citigroup Global Markets New Zealand Ltd., a Participant of the New Zealand Exchange Limited and regulated by the New Zealand Securities Commission. Level 19, Mobile on the Park, 157 lambton Quay, Wellington. The Product is made available in Poland by Dom Maklerski Banku Handlowego SA an indirect subsidiary of Citigroup Inc., which is regulated by Komisja Papierów Wartosciowych i Gield. Bank Handlowy w Warszawie S.A. ul. Senatorska 16, 00-923 Warszawa. The Product is made available in the Russian Federation through ZAO Citibank, which is licensed to carry out banking activities in the Russian Federation in accordance with the general banking license issued by the Central Bank of the Russian Federation and brokerage activities in accordance with the license issued by the Federal Service for Financial Markets. Neither the Product nor any information contained in the Product shall be considered as advertising the securities mentioned in this report within the territory of the Russian Federation or outside the Russian Federation. The Product does not constitute an appraisal within the meaning of the Federal Law of the Russian Federation of 29 July 1998 No. 135-FZ (as amended) On Appraisal Activities in the Russian Federation. 8-10 Gasheka Street, 125047 Moscow. The Product is made available in Singapore through Citigroup Global Markets Singapore Pte. Ltd., a Capital Markets Services Licence holder, and regulated by Monetary Authority of Singapore. 1 Temasek Avenue, #39-02 Millenia Tower, Singapore 039192. Citigroup Global Markets (Pty) Ltd. is incorporated in the Republic of South Africa (company registration number 2000/025866/07) and its registered office is at 145 West Street, Sandton, 2196, Saxonwold. Citigroup Global Markets (Pty) Ltd. is regulated by JSE Securities Exchange South Africa, South African Reserve Bank and the Financial Services Board. The investments and services contained herein are not available to private customers in South Africa. The Product is made available in Taiwan through Citigroup Global Markets Inc. (Taipei Branch), which is regulated by Securities & Futures Bureau. No portion of the report may be reproduced or quoted in Taiwan by the press or any other person. No. 8 Manhattan Building, Hsin Yi Road, Section 5, Taipei 100, Taiwan. The Product is made available in Thailand through Citicorp Securities (Thailand) Ltd., which is regulated by the Securities and Exchange Commission of Thailand. 18/F, 22/F and 29/F, 82 North Sathorn Road, Silom, Bangrak, Bangkok 10500, Thailand. The Product is made available in United Kingdom by Citigroup Global Markets Limited, which is regulated by Financial Services Authority. This material may relate to investments or services of a person outside of the UK or to other matters which are not regulated by the FSA and further details as to where this may be the case are available upon request in respect of this material. Citigroup Centre, Canada Square, Canary Wharf, London, E14 5LB. The Product is made available in United States by Citigroup Global Markets Inc, which is regulated by NASD, NYSE and the US Securities and Exchange Commission. 388 Greenwich Street, New York, NY 10013. Unless specified to the contrary, within EU Member States, the Product is made available by Citigroup Global Markets Limited, which is regulated by Financial Services Authority. Many European regulators require that a firm must establish, implement and make available a policy for managing conflicts of interest arising as a result of publication or distribution of investment research. The policy applicable to Citigroup Investment Research's Products can be found at www.citigroupgeo.com. Compensation of equity research analysts is determined by equity research management and Citigroup's senior management and is not linked to specific transactions or recommendations. The Product may have been distributed simultaneously, in multiple formats, to the Firm's worldwide institutional and retail customers. The Product is not to be construed as providing investment services in any jurisdiction where the provision of such services would be illegal. Subject to the nature and contents of the Product, the investments described therein are subject to fluctuations in price and/or value and investors may get back less than originally invested. Certain high-volatility investments can be subject to sudden and large falls in value that could equal or exceed the amount invested. Certain investments contained in the Product may have tax implications for private customers whereby levels and basis of taxation may be subject to change. If in doubt, investors should seek advice from a tax adviser. Advice in the Product has been prepared without taking account of the objectives, financial situation or needs of any particular investor. Accordingly, investors should, before acting on the advice, consider the appropriateness of the advice, having regard to their objectives, financial situation and needs.

citigroup

Equally, except to the extent to which the Product refers to website material of the Firm, the Firm takes no responsibility for, and makes no representations or warranties whatsoever as to, the data and information contained therein. Such address or hyperlink (including addresses or hyperlinks to website material of the Firm) is provided solely for your convenience and information and the content of the linked site does not in anyway form part of this document. Accessing such website or following such link through the Product or the website of the Firm shall be at your own risk and the Firm shall have no liability arising out of, or in connection with, any such referenced website.

ADDITIONAL INFORMATION IS AVAILABLE UPON REQUEST

Exhibit K

LEHMAN BROTHERS
EQUITY RESEARCH

January 30, 2006

United States of America
Healthcare
Medical Supplies & Devices

Bob Hopkins
1.212.526.4919
bhopkins@lehman.com

Boston Scientific (BSX - $ 23.15) 1-Overweight

Company Update

BSX: The Risks - Part 1

Investment Conclusion

- Over the course of this week we will be writing a series of notes highlighting four key risks facing BSX: intellectual property or patent risk, legal and legal liability risk, regulatory risk and integration risk. Each individual note will explore a different risk with today's note focusing on intellectual property risk.

Summary

- The purpose of these notes is to provide investors with more information to assess the risk profile of BSX as BSX's valuation and pending acquisition of GDT have created significant interest in the stock.

EPS ($) (FY Dec)

	2004	2005			2006			% Change	
	Actual	Old	New	St. Est.	Old	New	St. Est.	2005	2006
1Q	0.23A	0.51A	0.51A	0.51A	0.46E	0.46E	0.47E	122%	-10%
2Q	0.44A	0.48A	0.48A	0.48A	0.27E	0.27E	0.47E	9%	-44%
3Q	0.47A	0.42A	0.42A	0.42A	0.26E	0.26E	0.45E	-11%	-38%
4Q	0.49A	0.42E	0.42E	0.42E	0.29E	0.29E	0.48E	-14%	-31%
Year	1.63A	1.83E	1.83E	1.83E	1.29E	1.29E	1.85E	12%	-30%
P/E	14.2		12.7			17.9			

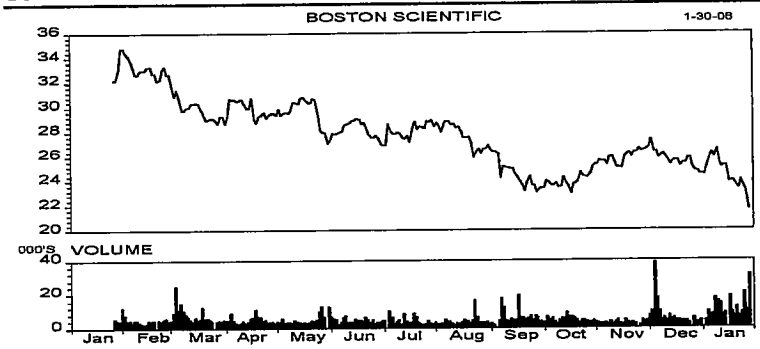
Market Data

Market Cap (Mil.)	20160
Shares Outstanding (Mil.)	840.00
Float (%)	574
Dividend Yield	N/A
Convertible	No
52 Week Range	35.26 - 22.80

Financial Summary

Revenue FY05 (Mil.)	6315.0
Five-Year EPS CAGR	16.0
Return on Equity	30.00
Current BVPS	4.64
Debt To Capital (%)	30.62

Stock Overview



Stock Rating		Target Price	
New:	1-Overweight	New:	$ 31.00
Old:	1-Overweight	Old:	$ 31.00

Sector View: 1-Positive

- Over the course of this week we will be writing a series of notes highlighting four key risks facing BSX: intellectual property or patent risk, legal and legal liability risk, regulatory risk and integration risk. Each individual note will explore a different risk with today's note focusing on intellectual property risk. On the legal risk front however, it is worth noting that over the weekend the New York Times reported that the US attorney's office in Minneapolis issued a subpoena for records disclosed in a Texas lawsuit that suggest the Government is undertaking a broad investigation of GDT including the potential for Medicare fraud. This is not surprising as we already knew the Government was interested, but the potential ramifications are meaningful and must be explored as we will later this week. The purpose of these notes is to provide investors with more information to assess the risk profile of BSX as BSX's valuation and pending acquisition of GDT have created significant interest in the stock.

- Intellectual Property Risk: As is typical in medical device land, BSX is involved in a number of litigations. Given that BSX is about to become a more highly leveraged company and that some of the current patent cases involve BSX's most important pipeline products,

the stakes are higher than normal. To bottom line it, we believe BSX's IP risk is manageable despite our view that BSX is more likely than not to come up on the short-end on a number of key upcoming decisions including Ding. We should hear a key decision on the Ding patent sometime in the next few months. Most of the key patent cases that BSX faces today involve JNJ and include the Palmaz-Schatz litigation, the Ding litigation, the Grey litigation, the Jang litigation, the Grainger litigation and a number of others. There are even hypothetical litigations to contend with as JNJ has strongly suggested that they feel GDT and ABT may violate JNJ/Wyeth DES patents covering the "limus" family of drugs. BSX has not reserved any meaningful amount of money for currently pending IP litigation. The upcoming ruling on Ding from Judge Robinson of Delaware is the most important as a BSX victory would not only increase the probabilities that Liberte could launch without a problem, but it might also have a positive impact on the amount that BSX ultimately pays JNJ on the Palmaz litigation. If the Ding decision goes against BSX, investors would assume Liberte may never come to market, which would be a negative for investor sentiment towards BSX but it would not change our current BSX EPS estimates by more than a few pennies as we feel the market share loss relative to our current model would be less than 5 points. Liberte is a potential source of upside, but most seem to have modeled it conservatively.

- Importantly, it is our opinion that BSX faces little potential liquidity risk from these litigations as most of these law suits involve future products that have yet to truly launch in the US, which suggests little potential for damages. The Palmaz litigation could involve $500mm-$1bln in damages to JNJ, but that is something that investors have been aware of for a long time and we believe is manageable. The Ding ruling is critical because if BSX losses, BSX may not be able to launch its next generation DES (Liberte) in the US. Because BSX will now potentially have access to GDT's Xience stent however, the risk to BSX from not having Liberte is somewhat mitigated in our view especially considering that JNJ's pipeline remains an unknown and that JNJ Palmaz patents expired last year. We believe Judge Robinson will most likely overturn the Jury decision on Ding and hand JNJ a victory for reasons that we explain in the note, and while this will create considerable noise in the market place, our 2007 BSX EPS number of $1.47 would decline by less than $0.05. Liberte is scheduled to come to market late Q3 or early Q4 of this year and Xience is due out Q3:07. See the attached note for full details on all litigations.

BSX Litigation: An Overview

In the following sections, we outline the majority of outstanding patent cases between JNJ and BSX on bare metal and drug-eluting stent technology, discussing those decisions that have gone in favor of BSX and JNJ and those yet to be decided. In addition, we attempt to quantify the potential damages BSX may owe JNJ, which could total as much as $900 mm ($550 mm or so for Express and Liberte and $350 mm for infringement by the NIR stent) in retro- and prospective royalties, by our calculations. However, if BSX is victorious on Ding, we believe it would swing the leverage back to BSX and any damages would likely be minimized if the two parties decide to trade IP rights (and money) in exchange for a settlement. If BSX loses on Ding, BSX's access to the Xience stent via the GDT merger would prevent any real market share damage in our view and while the economics to BSX from Xience sales are much less than from any TAXUS sales, we have taken this into account in our models.

IP Summary – What you Need To Know

Essentially all DES manufacturers have been found in violation of JNJ's Palmaz-Schatz patent and BSX is no exception. While this patent has expired, we are waiting for the damages phase to hear how much BSX will owe JNJ for sales of its Express stents before the expiration. We estimate between $500mm and $1bln could be owed. BSX's Liberte stent has also been found to be in violation of JNJ's Gray patent, but JNJ's Cypher stent has been found to violate BSX's Ding patent and if that ruling sticks, BSX would have a great deal of leverage over JNJ, which could limit the amount BSX has to pay JNJ on Palmaz and limit JNJ's ability to shut down Liberte. A horse trade would be likely in that situation. BSX's Ding patent describes the use of a topcoat in a DES polymer and a jury ruled late last year that JNJ's Cypher DES system violates this key patent. Cypher is the only DES system JNJ sells. In addition to planning an appeal on Ding, JNJ is asking the Judge overseeing the case to overturn the Jury verdict and throw out the decision. If the Judge overturns the Jury verdict BSX's Liberte stent would be at risk because BSX's leverage over the Gray ruling would go away. JNJ has also been found to violate the Jang patent, but BSX's right to Jang seems in doubt. The damages phase on Palmaz seems to be on hold until the Ding decision.

Outside of Ding, Jang, Gray and Palmaz, BSX is also suing JNJ in the US on the Grainger patent, which describes the use of systemic drugs delivered on a stent. The case was originally scheduled to be heard in October (by Judge Robinson), but has since been rescheduled for March of 2006. JNJ has also made some recent assertions that GDT's everolimus may infringe JNJ IP covering the use of limus compounds (JNJ uses the parent compound, Sirolimus) in DES platforms, however none of those patents have been litigated and, to our knowledge, no suits have been filed as of yet. Also worth mentioning, BSX has been victorious in Europe on IP, effectively forcing JNJ to shift manufacturing out of the Netherlands, but this transition appears to have occurred seamlessly and therefore we doubt it provides BSX any significant leverage. Also worth mentioning, BSX has agreed to pay Medinol $750 mm in damages relating to the NIR stent – the settlement provides an end to most of the litigation risk, though there are still outstanding cases by both parties that were not included in the settlement.

In summary, BSX has won the initial rounds of litigation against JNJ on two important US patents – Ding and Jang, which cover polymer coatings for DES and bare metal stent architecture, respectively. JNJ has been victorious on the Palmaz-Schatz and Gray patents, which describe bare metal stent architecture – Express2 violates Palmaz, while Liberte violates both. Importantly, Palmaz-Schatz expired in November of 2005, but the Gray patent will be enforceable until 2016. The court has yet to decide on infringement for Liberte DES because it has yet to be launched in the US, but given that Liberte DES is, in effect, the Liberte stent, we believe there is a high probability Liberte DES (as well as Barracuda, which has the same stent architecture) will infringe Gray.

With respect to timing, the key events we are waiting for are: 1) Judge Robinsons' decision on motions to overturn jury rulings on Ding and Jang as well as BSX motions to overturn Palmaz and Gray, with Ding being the key and JNJ having a reasonable chance of prevailing, in our opinion. No dates have been set, but final briefs were filed in October of 2005 and a ruling could come at any point; 2) JNJ is awaiting reinstatement of a $342 mm damages ruling for BSX's infringement with the NIR stent; 3) following the motions to overturn, all these cases will enter damages phases, with monetary awards to be decided and 4) all these decisions will be appealed, and importantly, BSX has not reserved for any of the potential damages for each of these cases.

BSX Wins: The Ding and Jang Patents

On July 2nd 2005, a jury handed down a surprising victory to BSX by ruling that JNJ's Cypher drug-eluting stent, among others, infringes BSX's Ding and Jang patents; the jury also ruled that the patents were valid. Ding describes a polymer with a top coat while Jang covers specific stent geometry. Please see Figures 1 and 2 below for specific patent details and wording.

Figure 1: BSX Patent Wins

Key Patents Under Litigation

Patent Assignee	Patent No.	Date of Filing	Date of Issue	Inventor	Title	Abstract
BSX	6,120,536	6/13/1996	9/19/2000	Ding	Medical devices with long-tern non-thrombogenic coatings	A coating and method for implantable open lattice metallic stent prostheses are disclosed. The coating includes a relatively thin layer of biostable elastomeric material containing an amount of biologically active material, particularly heparin, dispersed in the coating in combination with a non-thrombogenic surface. In one embodiment, the surface is provided with sites of high electronegativity species by coating with fluorosilicone which aid in controlling elution, particularly the initial release rate, and reduced thrombogenic activity. Other non-thrombogenic outer layers for heparin such as covalently bound polyethylene glycol (PEG) are also disclosed.
BSX	5,922,021	4/25/1997	7/13/1999	Jang	Intravascular stent	A stent in a non-expanded state has a first expansion strut pair consisting of a first expansion strut positioned adjacent to a second expansion strut and a joining strut which couples the first and second expansion struts at a distal end of the first expansion strut pair. A plurality of the first expansion strut pair form a first expansion column. A second expansion strut pair consists of a first expansion strut positioned adjacent to a second expansion strut and a joining strut couples the first and second expansion struts at a proximal end of the second expansion strut pair. A plurality of the second expansion strut pair form a second expansion column. A first connecting strut includes a first connecting strut proximal section, a first connecting strut distal section and a first connecting strut intermediate section. The first connecting strut proximal section is coupled to the distal end of the first expansion strut pair in the first expansion column and the first connecting strut distal section is coupled to the proximal end of the second expansion strut pair of the second expansion column. A plurality of the first connecting struts form a first connecting strut column that couples the first expansion column to the second expansion column. A length of the first connecting strut proximal section is equal to a length of the first connecting strut distal section, and a length of the first connecting strut intermediate section is greater than the length of the first connecting strut proximal and distal sections.

Source: US Patent Office

Figure 2: Key Ding Patent Claims

Key Ding Patent Claims Under Litigation (BSX Patent No. 6,120,536)

Claim No.	Description
1	A medical device having at least a portion which is implantable into the body of a patient, wherein at least a part of the device portion is metallic and at least part of the metallic device portion is covered with a coating for release of at least one biologically active material, wherein said coating comprises an undercoat comprising a hydrophobic elastomeric material incorporating an amount of biologically active material therein for timed release therefrom, and wherein said coating further comprises a topcoat which at least partially covers the undercoat, said topcoat comprising a biostable, non-thrombogenic material which provides long term non-thromobogenicity to the device portion during and after release of the biologically active material, and wherein said topcoat is substantially free of an elutable material.
6	The device of claim 1 wherein the medical device is an expandable stent.
8	The device of claim 6 wherein the stent comprises a tubular body having open ends and an open lattice sidewall structure and wherein the coating conforms to said sidewall structure in a manner that preserves said open lattice.

Source; U.S. Patent Office web site

JNJ's Prospects for Appeal on Ding

Following the jury's decision on Ding, JNJ filed a motion with Judge Robinson to vacate the ruling based both on the narrow definition of important terms in claim 1 (see Figure 2 above), particularly the meaning of elastomeric, as well as the existence of prior art. Though the jury found that Ding was valid and JNJ did infringe, we continue to believe JNJ has several valid arguments that could serve the basis for a strong appeal and while there has been precedent for a Judge to overrule a decision from the bench, the likelihood of this occurring seems low. Specifically, in our review of the patent and the comments/rulings by Judge Robinson prior to the decision, we believe JNJ will again

argue in its appeal that it does not infringe Ding, citing, among other things, the very specific definition of elastomeric coatings. In the Markman hearings (claims construction), an "elastomeric" material was defined by Judge Robinson as "a material able to stretch or expand without breaking, and to return to its original dimensions." JNJ has previously described Cypher as having an elastomeric coating, however during the trial, the company presented evidence which Judge Robinson cited in her decision that the coating does indeed crack when the stent is expanded – Judge Robinson, in her decision, specifically stated uncertainty as to whether, by the letter of the law, such a narrow definition would be inclusive of JNJ's stent. Despite the Jury's ruling, JNJ may continue to use this argument in its appeal. With respect to prior art, several patents describing polymers on stents do exist (Fox, Domb, Myler), however with BSX having now received two affirmations of validity (from the patent office and Friday's jury decision), the probability the patent is found to be invalid would seem low.

Other Litigation: BSX's Grainger Patent

Finally, March of 2006, JNJ and BSX will go back to trial once again to litigate the next IP case over BSX's Grainger patent (6,251,290), which describes the systemic (oral administration) and site-specific (on a stent) usage of therapeutic compounds (tamoxifen derivatives) to treat cardiovascular disease. No updates have been given and timing of a ruling is unclear, other than to say Judge Robinson will likely rule on the outstanding cases (Ding, Gray, Palmaz, etc) prior to rendering a decision on Grainger.

JNJ's Wins: Palmaz-Schatz and Gray and the NIR stent

On June 21st, 2005 a U.S. jury in the federal court of Delaware found that BSX's Express2 and Liberte bare metal stents and Taxus drug-eluting stent infringe JNJ's Palmaz-Schatz patent (expired in November 2005) and that Liberte also infringes JNJ's Gray patent (expires in 2016). The finding of infringement on the Palmaz-Schatz patent is not unexpected and the damages phase of the trial will be set after Judge Robinson rules on motions to overturn the jury decisions on Ding, Jang, Palmaz and Gray. The ruling on the Gray patent gives JNJ some meaningful leverage as it could allow JNJ to seek an injunction on BSX's Liberte DES platform or at least seek a royalty on Liberte DES sales when that device is approved around mid-2006, although BSX would be free to revert to the GDT Xience V stent.

In addition, on March 24, 2005 JNJ was victorious in a multi-year battle against BSX involving the NIR stent. JNJ originally won in 2000, but the court set aside the decision in 2002 and sent it back to trial which finally decided in JNJ's favor in March. JNJ is seeking reinstatement of the original $324 mm damages awarded (plus interest). This decision could come any day.

Damages on Palmaz and Ding: What could BSX Have to Pay?

Assuming BSX loses on Ding and has little to no leverage in settlement/cross-licensing negotiations, we calculate that BSX could owe JNJ approximately $900 mm, comprised of $342 mm (plus interest) on NIR, and $550 mm for Express and Liberte. The latter could be reduced (perhaps to $200-300 mm) if BSX launches Xience in 2007 and continues selling Express2 (and not Liberte) which violates only the expired Palmaz patent, not Gray. Figure 3 below lays out the calculation damages. Our calculation involves applying a 15% royalty rate (an amount equivalent to that paid by GDT to JNJ in a similar ruling) to both Taxus and Express 2/Liberte sales from launch. On Taxus damages, we apply the royalty to only the bare metal portion of the stent as Gray and Palmaz only cover bare metal stent architecture. Of note, JNJ could seek treble damages award for willful infringement on Palmaz and Gray, which could bring the award well north of $1 billion, but the hurdle for such an outcome is high, in our opinion.

Figure 3: BSX Potential Payments to JNJ

BSX Payment to JNJ Cumulative BMS + DES Sales	2002A	2003A	2004A	2005A	2006E	2007E	2008E	Total
US Revenues ($MM)								
Express/Liberte BMS	$90	$209	$60	$27	$16	$15	$15	$432
TAXUS/Liberte DES	0	0	1,571	1,762	1,660	1,933	1,125	8,051
Total	$90	$209	$1,632	$1,789	$1,676	$1,948	$1,140	$8,483
ASPs ($)								
Express/Liberte BMS	$1,050	$915	$910	$910	$850	$850	$850	$931
TAXUS/Liberte DES	$0	$0	$2,580	$2,450	$2,260	$2,050	$1,900	$2,238
Unit Sales								
Express/Liberte BMS	85,519	227,869	66,264	29,670	18,824	17,647	17,647	463,440
TAXUS/Liberte DES	0	0	609,070	719,184	734,513	942,927	592,105	3,597,799
Total	85,519	227,869	675,334	748,854	753,337	960,574	609,752	4,061,238
Adjusted Revenues ($MM)								
Express/Liberte BMS	$90	$209	$60	$27	$16	$15	$15	$432
TAXUS/Liberte DES	0	0	554	654	624	801	503	3,138
Total	$90	$209	$615	$681	$640	$816	$518	$3,569
Royalty Assumption	15%	15%	15%	15%	15%	15%	15%	15%
Royalties on Express	$14	$32	$95	$106	$0	$0	$0	$247.0
Royalties on Liberte	$0	$0	$0	$0	$99	$126	$80	$305.9
Total Royalties Due ($MM)	$13.9	$32.3	$95.2	$105.6	$99.2	$126.5	$80.3	$552.9

Source: Company data; Lehman estimates

Analyst Certification:

I, Bob Hopkins, hereby certify (1) that the views expressed in this research Company Note accurately reflect my personal views about any or all of the subject securities or issuers referred to in this Company Note and (2) no part of my compensation was, is or will be directly or indirectly related to the specific recommendations or views expressed in this Company Note.

Other Team Members:

Blackman, Mathew	1.212.526.9955	mblackma@lehman.com
Guha, Amrita	1.212.526.5144	aguha@lehman.com

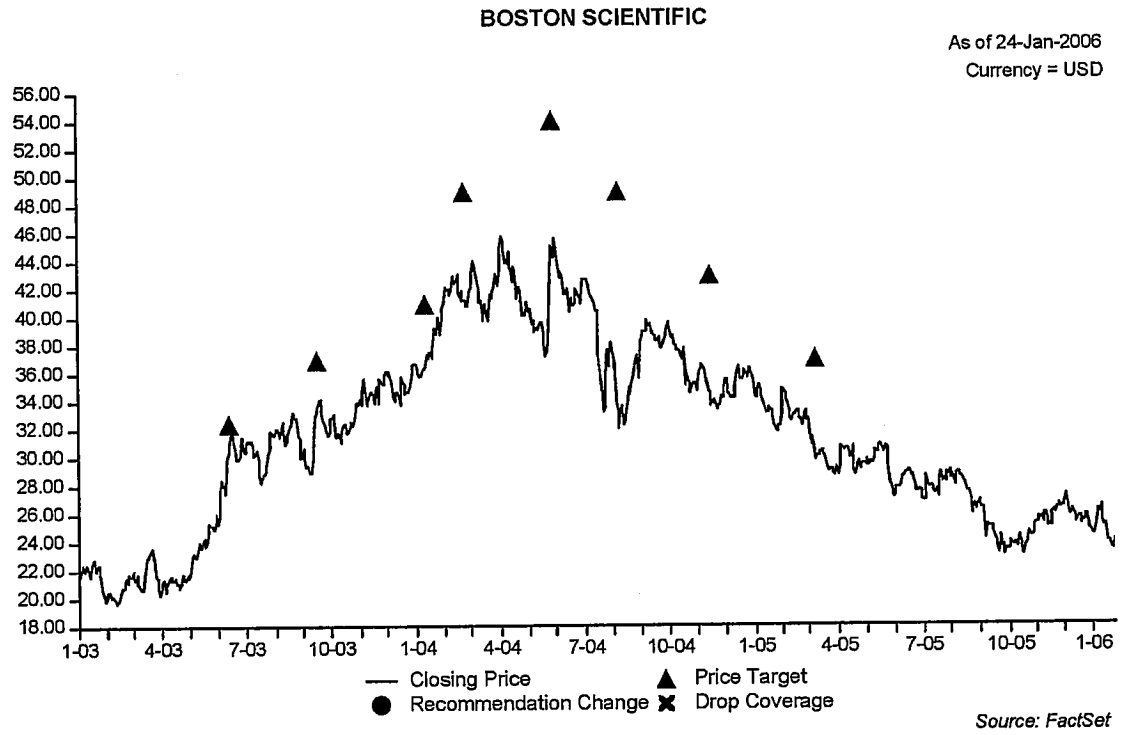
Company Description:

Boston Scientific is a global medical technology company focused on less invasive medicine, specifically interventional cardiology, radiology, neurology, and urology products.

Important Disclosures:

Boston Scientific (BSX) **$ 23.15 (26-Jan-2006)** **1-Overweight / 1-Positive**

Rating and Price Target Chart:



Currency=$

Date	Closing Price	Rating	Price Target
09-Mar-05	29.75		37.00
15-Nov-04	34.60		43.00
06-Aug-04	33.21		49.00
28-May-04	44.30		54.00
24-Feb-04	41.27		49.00

Date	Closing Price	Rating	Price Target
12-Jan-04	36.40		41.00
16-Sep-03	33.25		37.00
12-Jun-03	30.43		32.50

FOR EXPLANATIONS OF RATINGS REFER TO THE STOCK RATING KEYS LOCATED ON THE PAGE FOLLOWING THE LAST PRICE CHART.

One of the analysts on the coverage team (or a member of his or her household) owns shares of the common stock of Boston Scientific. Lehman Brothers Inc and/or an affiliate trade regularly in the shares of Boston Scientific.

Valuation Methodology: Our $31 price target is derived from a 18.5x multiple off our 2008 cash EPS estimate of $1.68.

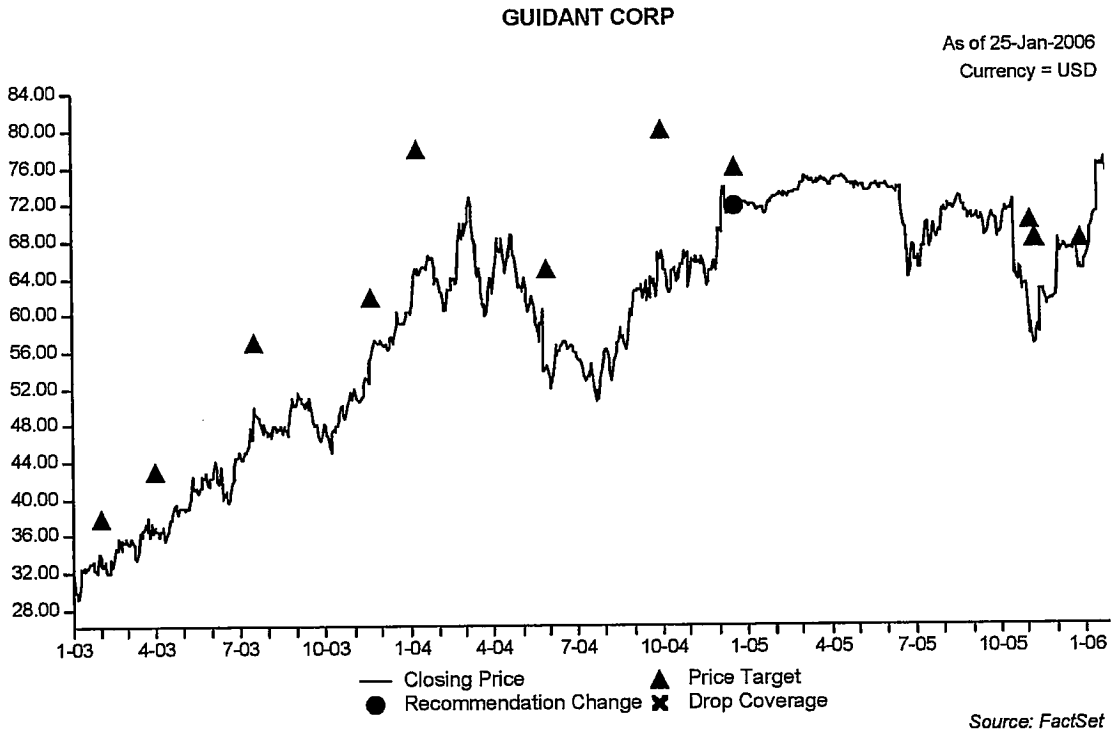
Risks Which May Impede the Achievement of the Price Target: Exposure to emerging drug-eluting stent market. Exposure to interventional cardiology market. Competition from other drug-eluting stent players. Acquisition integration. Risk from pending litigation.

Other Material Conflicts: One of the analysts on the coverage team (or a member of his or her household) owns common stock and options in the common stock of Boston Scientific.

Important Disclosures Continued:

Guidant Corp (GDT) **$ 75.26 (26-Jan-2006)** **2-Equal weight / 1-Positive**

Rating and Price Target Chart:



Currency=$

Date	Closing Price	Rating	Price Target
29-Dec-05	64.85		68.00
10-Nov-05	57.75		68.00
08-Nov-05	56.53		68.00
03-Nov-05	57.57		70.00
21-Dec-04	71.70		76.00
21-Dec-04	71.70	2-Equal weight	
01-Oct-04	66.76		80.00

Date	Closing Price	Rating	Price Target
28-May-04	54.34		65.00
12-Jan-04	64.96		78.00
20-Nov-03	55.35		62.00
17-Jul-03	49.96		57.00
02-Apr-03	36.48		43.00
31-Jan-03	33.62		38.00

FOR EXPLANATIONS OF RATINGS REFER TO THE STOCK RATING KEYS LOCATED ON THE PAGE FOLLOWING THE LAST PRICE CHART.

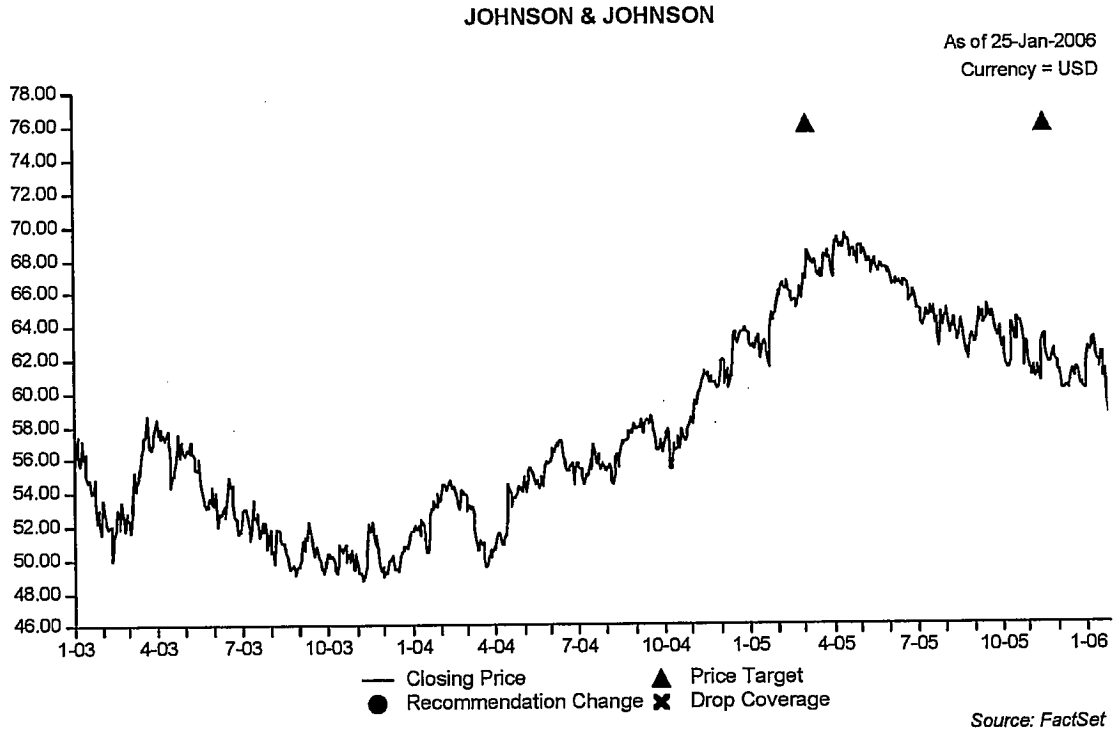
Lehman Brothers Inc. and/or its affiliates beneficially owns 1% or more of any class of common equity securities of Guidant Corp as of the end of last month.
Lehman Brothers Inc and/or an affiliate trade regularly in the shares of Guidant Corp.

Risks Which May Impede the Achievement of the Price Target: Exposure to emerging drug-eluting stent market. Exposure to cardiac rhythm management market.

Important Disclosures Continued:

Johnson & Johnson (JNJ) **$ 58.64 (26-Jan-2006)** **1-Overweight / 1-Positive**

Rating and Price Target Chart:



Currency=$

Date	Closing Price	Rating	Price Target
17-Nov-05	63.34		76.00

Date	Closing Price	Rating	Price Target
07-Mar-05	68.44		76.00

FOR EXPLANATIONS OF RATINGS REFER TO THE STOCK RATING KEYS LOCATED ON THE PAGE FOLLOWING THE LAST PRICE CHART.

Lehman Brothers Inc and/or an affiliate trade regularly in the shares of Johnson & Johnson.

Risks Which May Impede the Achievement of the Price Target: Risks to the JNJ story include possible rotation back into large-cap pharma, delays and/or failure in the late-stage pharma pipeline, regulatory and integration risks associated with the GDT acquisition, and a marked slowdown in the consumer business, which has been growing well above historical rates for the past two years.

Important Disclosures Continued:
The analysts responsible for preparing this report have received compensation based upon various factors including the firm's total revenues, a portion of which is generated by investment banking activities

Company Name	Ticker	Price (26-Jan-2006)	Stock / Sector Rating
Boston Scientific	BSX	$ 23.15	1-Overweight / 1-Positive

Related Stocks	Ticker	Price (26-Jan-2006)	Stock / Sector Rating
Guidant Corp	GDT	$ 75.26	2-Equal weight / 1-Positive
Johnson & Johnson	JNJ	$ 58.64	1-Overweight / 1-Positive

Sector Coverage Universe
Below is the list of companies that constitute the sector coverage universe against which the primary stock, Boston Scientific, is rated:
Alcon, Inc (ACL)
Bausch & Lomb (BOL)
Boston Scientific (BSX)
DJ Orthopedics (DJO)
Guidant Corp (GDT)
Medtronic Inc (MDT)
Nuvasive Inc (NUVA)
Stryker Corp (SYK)
Thoratec Corp (THOR)
Zimmer Holdings (ZMH)
Angiotech Pharmaceuticals (ANPI)
Biomet, Inc (BMET)
Conor Medsystems (CONR)
Greatbatch Inc. (GB)
Johnson & Johnson (JNJ)
Novoste Corp (NOVTD)
St. Jude Medical (STJ)
Syneron Medical (ELOS)
Wright Medical Group (WMGI)

Guide to Lehman Brothers Equity Research Rating System:
Our coverage analysts use a relative rating system in which they rate stocks as 1-Overweight, 2-Equal weight or 3-Underweight (see definitions below) relative to other companies covered by the analyst or a team of analysts that are deemed to be in the same industry sector (the "sector coverage universe"). To see a list of the companies that comprise a particular sector coverage universe, please go to www.lehman.com/disclosures

In addition to the stock rating, we provide sector views which rate the outlook for the sector coverage universe as 1-Positive, 2-Neutral or 3-Negative (see definitions below). A rating system using terms such as buy, hold and sell is not the equivalent of our rating system. Investors should carefully read the entire research report including the definitions of all ratings and not infer its contents from ratings alone.

Stock Rating
1-Overweight - The stock is expected to outperform the unweighted expected total return of the sector coverage universe over a 12-month investment horizon.
2-Equal weight - The stock is expected to perform in line with the unweighted expected total return of the sector coverage universe over a 12- month investment horizon.
3-Underweight - The stock is expected to underperform the unweighted expected total return of the sector coverage universe over a 12-month investment horizon.
RS-Rating Suspended - The rating and target price have been suspended temporarily to comply with applicable regulations and/or firm policies in certain circumstances including when Lehman Brothers is acting in an advisory capacity in a merger or strategic transaction involving the company.

Sector View
1-Positive - sector coverage universe fundamentals/valuations are improving.
2-Neutral - sector coverage universe fundamentals/valuations are steady, neither improving nor deteriorating.
3-Negative - sector coverage universe fundamentals/valuations are deteriorating.

Distribution of Ratings:
Lehman Brothers Equity Research has 1836 companies under coverage.
42% have been assigned a 1-Overweight rating which, for purposes of mandatory regulatory disclosures, is classified as Buy rating, 36% of companies with this rating are investment banking clients of the Firm.
41% have been assigned a 2-Equal weight rating which, for purposes of mandatory regulatory disclosures, is classified as Hold rating, 6% of companies with this rating are investment banking clients of the Firm.
17% have been assigned a 3-Underweight rating which, for purposes of mandatory regulatory disclosures, is classified as Sell rating, 75% of companies with this rating are investment banking clients of the Firm.

Exhibit L

Link to full report including important disclosures*
http://rsch1.ml.com/9093/24013/ds/2768242_.PDF

New JNJ stent manufacturing now coming on line
The first manufacturing line for Johnson & Johnson's (JNJ;A-1-7;$59.29) Cypher drug eluting stent (DES) is scheduled to come on line this month with one line per month to be added over the next 3 months. With the new Cypher capacity, JNJ expects to realize share gains over the next few quarters. Of the ~1,600 U.S. interventional cardiology labs, JNJ estimates it has a presence in ~800 of which 500 get preferential allocation of Cypher. In those 500 targeted accounts, JNJ pegs its DES market share at upwards of 60%.

JNJ-GDT co-promotion agreement could remain in place
The pending sale of Guidant's (GDT;RSTR;$77.55) Vascular Intervention franchise to Abbott (ABT;B-1-7;$45.16) in conjunction with Boston Scientific's (BSX;B-2-9; $22.95) pending purchase of Guidant does not void the existing JNJ-GDT co-promotion agreement for Cypher. JNJ has indicated that it will review the arrangement post closing of the deal, which could result in a cessation of the arrangement or a continuation pending the approval of Guidant's Xience DES in the U.S. (late 2007/ early 2008).

New DES products expected in 2007 from JNJ
In early '07, JNJ expects to launch the Cypher Select in Europe with an enhanced delivery system to be followed with Cypher in 2.25mm and 4.00mm diameters. Next up in the U.S. is the Cypher Nxt, which is Cypher on GDT's Vision delivery system. Further back in the queue is: 1) Project Python, a new stent/delivery system (U.S.) , 2) Cypher Neo, a cobalt chrome DES based on a new stent design/delivery system (WW) and 3) Firefox, a cobalt chrome DES based on a new stent/delivery system which is characterized as a "workhorse" stent that will also be targeted at small vessels. And as part of the JNJ-GDT cross-licensing agreement, JNJ has rights to GDT's bioabsorbable DES (enrollment in the ABSORB trial evaluating GDT's bioabsorbable stent is underway).

More legal wrangling from JNJ possible
JNJ has two patents (Wright and Falotico), which appear to relate to the elution characteristics of "olimus" compounds; JNJ's Cypher DES uses sirolimus, a member of the olimus family of drugs; other olimus drugs include Guidant's everolimus and Abbott/Medtronic's zotarolimus (ABT-578). The European launch of Guidant's Xience DES, which the company has targeted for Q2:06, could trigger possible legal activity since we understand U.S. patent law prohibits domestic manufacture of a product for sale outside the U.S. if there's been infringement of intellectual property.

To reply to Katherine Martinelli directly, Click here
mailto:katherine_martinelli@ml.com or call +1 617 350 5862

Exhibit M

The International Herald Tribune

January 23, 2006 Monday

SECTION: FINANCE; Pg. 12

LENGTH: 750 words

HEADLINE: J&J works to discredit rival offer for Guidant;
MARKETPLACE by Bloomberg

BYLINE: Avram Goldstein

DATELINE: WASHINGTON

BODY:

Johnson & Johnson, facing a deadline on Tuesday for raising its bid to acquire the cardiac device maker Guidant, is trying to sow doubts among investors about Boston Scientific's rival offer, according to analysts.

Johnson & Johnson, the world's biggest maker of medical devices, and its advisers told securities analysts last week that Boston Scientific would borrow too much for the deal, according to analysts at Prudential Equity Group and A.G. Edwards.

J&J also said Boston Scientific had been making unrealistic financial projections to justify its $27 billion offer to buy Guidant, almost $3 billion more than Johnson & Johnson's.

"J&J is communicating to the Street that Boston Scientific's $80-a-share offer for Guidant is fraught with uncertainty," Lawrence Biegelsen, an analyst with Prudential in New York, said in a note to clients sent on Friday. The campaign, he said, suggests "that J&J is still very interested in acquiring Guidant and that J&J will likely increase its offer at least one more time."

The Guidant transaction would be the biggest purchase of a medical device company. Guidant, the second-largest maker of implantable defibrillators and pacemakers, behind Medtronic, is developing a cardiac stent that would pose a competitive threat to rival products of J&J and Boston Scientific, the world's biggest maker of heart stents, tiny metal sleeves used to clear artery blockages.

A spokesman for J&J, Jeffrey Leebaw, and for Guidant, Steven Tragash, declined to comment.

J&J shares fell $1.37, or 2.2 percent, to close last week at $60.80 in New York Stock Exchange composite trading. Guidant dropped 17 cents, to $75.95. Boston Scientific declined 36 cents, or 1.5 percent, to close at $23.59.

Guidant said Tuesday that Boston Scientific's offer of about $27 billion, or $80 a share, of which $42 would be in cash and $38 in stock, was "superior" to J&J's bid of $24.2 billion, or $71 a share, consisting of $40.52 in cash and the rest in J&J shares.

Johnson & Johnson's campaign consists of telling analysts and shareholders that Boston Scientific is in over its

head and is tempting patent litigation that may undercut Boston Scientific's plans.

"They're trying to tell all of us that there are patents out there that they have that they feel can stop Boston Scientific," said Jan David Wald, an analyst with A.G. Edwards. Wald said he had been called by a Johnson & Johnson employee, whom he declined to name.

Johnson & Johnson told analysts it was considering filing patent infringement lawsuits over stent drug coatings to keep Boston Scientific and its bidding partner, Abbott Laboratories, from profiting from the new Guidant devices, according to Biegelsen of Prudential.

Drug coatings on stents are designed to keep tissue growth from clogging blood vessels again.

Abbott agreed to contribute $6.4 billion to the Boston Scientific bid and acquire Guidant's vascular business including the new cardiac stent.

Abbott shares lost $1.19, or 2.9 percent, on Friday to close the week at $40.35.

Patent infringement lawsuits over stent drug coatings have "no bearing on our proposed acquisition of Guidant," a spokesman for Boston Scientific, Paul Donovan, said. "Unfortunately, threats of legal action are commonplace in our industry."

Boston Scientific and J&J have been fighting in court for years over patent-infringement cases related to stent design. At the moment, the two companies are alone in the U.S. stent market, with Boston Scientific holding a 55 percent share.

Abbott, Guidant and Medtronic are all developing competing products coated with drugs similar to the one that Johnson & Johnson's stent uses.

The potential for Johnson & Johnson to prevent Abbott and Boston Scientific from marketing Guidant's next-generation heart stent "could give the Guidant board pause for approving a Boston Scientific-Guidant merger," Biegelsen said. "J&J claims that two of its patents may be infringed if a company tries to launch a drug-eluting stent coated with" Abbott's zotarolimus and Guidant's everolimus, he wrote.

After the Guidant board declared Boston Scientific's bid superior, Johnson & Johnson issued a statement calling the proposal a "highly dilutive and leveraged transaction based on extremely aggressive business projections."

The statement said the Boston Scientific bid "will not provide $80 per share in value to Guidant shareholders."

Boston Scientific initially bid $25 billion on Jan. 8, a month after declaring its intention to make an offer.

LOAD-DATE: January 23, 2006

Exhibit N

SUITORS TAKE GUIDANT FIGHT TO THE STREET The Boston Globe January 20, 2006 Friday

The **Boston Globe**

January 20, 2006 Friday
THIRD EDITION

SECTION: BUSINESS; Pg. C1

LENGTH: 721 words

HEADLINE: SUITORS TAKE GUIDANT FIGHT TO THE STREET

BYLINE: BY STEPHEN HEUSER, GLOBE STAFF

BODY:

With the clock ticking down for Johnson & Johnson to answer Boston Scientific's $27 billion bid for Guidant Corp., the two rivals are trying to torpedo each other's bids with Wall Street analysts and major stockholders.

Three days ago Guidant declared Boston Scientific's new offer superior, giving the Natick device maker the upper hand for the first time in a six-week bidding war. Under terms of Guidant's existing deal with Johnson & Johnson, the company has until Tuesday to boost its offer or lose Guidant.

As the day approaches, Johnson & Johnson has been raising questions about the solidity of Boston Scientific stock and the likelihood the much smaller company can actually close the deal, said two analysts who have been contacted by the firm.

Boston Scientific, to support its bid, released a set of slides on Wednesday showing a crisp month-by-month march to a completed merger and outlining plans to exceed Wall Street's earnings estimates.

"It's behind closed doors right now," said Thomas Gunderson, a medical device analyst for Piper Jaffray, of the bidding war for Guidant. "It's like watch ing a tennis match, but the ball has to pass through this 20-foot blind spot before the audience gets to see how the ball comes out the other side, if it comes at all."

Gunderson said he had not been contacted by Johnson & Johnson, but had a conversation with Boston Scientific earlier this week.

After more than a month of back-and-forth public statements, filings, and conference calls, the intense lobbying by both companies this week underscores their delicate positions in the bidding war over Guidant

When Guidant's board of directors picked Boston Scientific's offer on Tuesday, Johnson & Johnson found itself out in the cold for the first time since it signed a deal to buy Guidant more than a year ago, and now must decide whether to re-enter the contest.

"I suspect that they're trying to determine what a winning bid is, and secondarily do they want to go that

high," said Robert Faulkner, an analyst for JMP Securities.

With a reputation for fiscal caution, Johnson & Johnson could be hesitant to make any bid over $76 a share, the price it offered for Guidant in December 2004, before Guidant suffered a series of product recalls that pushed its value down.

A key concern for Boston Scientific, on the other hand, is the price of its own stock. Its $80 bid comprises $42 in cash and $38 in Boston Scientific stock, but because of a "collar" provision in the offer, the value of that bid will drop sharply if Boston Scientific stock slides below $22.62 a share. Even if it gets close to that number, many investors' models will begin assigning a lower value to the bid, and Johnson & Johnson could woo Guidant back with a lower bid.

Boston Scientific stock dropped by more than $1 on Tuesday when it made its $80-per-share offer, but has been largely steady since then at just under $24 a share. It closed at $23.95 last night, up 1 cent on the day.

Johnson & Johnson launched its first salvo on Tuesday night, after Guidant gave the nod to Boston Scientific. In an unusually terse statement, the New Jersey healthcare giant attacked the fundamental value of the Boston-Guidant deal, calling it "based on extremely aggressive business projections."

Since then, the company has raised similar questions in phone conversations with analysts who value medical device companies. It has also raised the prospect that it could use patents and existing ties to Guidant to derail or complicate Boston Scientific's offer, said Matthew Dodds, an analyst for Citigroup who is skeptical about Guidant's value to both companies.

Johnson & Johnson is "strongly suggesting" that it could tie up the deal past Boston's estimated completion date of March 31, he said, and questioned the business estimates it is based on.

"They're talking about the excessiveness of the Boston Scientific deal, how they don't believe the numbers can work," he said.

Contacted for this story, Johnson & Johnson would not discuss details of its conversations with investors.

A Boston Scientific spokesman said the deal at this point would come down to the numbers.

"We're at $80, and J&J is at $71," he said. "Guidant has declared us superior, and we're working very hard to close this deal as soon as possible."

Stephen Heuser can be reached at sheuser@globe.com.

GRAPHIC: PHOTO

LOAD-DATE: January 20, 2006

Exhibit O

Abbott stock falls on concerns over success of Guidant bid

By Paul Merrion
Jan. 20, 2006

(Crain's) — Abbott Laboratories stock took a tumble today after a research analyst raised the possibility that Abbott and another company, Boston Scientific Corp., may not win the bidding for Guidant Corp.

The analyst, Prudential Equity Group, LLC's Larry Biegelsen, reported that Guidant's board could balk at Boston Scientific and Abbott's joint bid because Johnson & Johnson, a competing bidder for Guidant, claims its patents would be violated if Abbott markets its own drug-eluting stents or those made by Guidant. That could give Guidant's board pause in approving Boston Scientific's bid, Mr. Biegelsen wrote.

Abbott's shares closed down $1.19, or 2.9%, to $40.35 on Friday, capping two weeks of declines that wiped out a 3.7% gain Jan. 9, when investors bid up Abbott's stock on enthusiasm for the potential deal.

Since the bid was announced, Abbott has raised its offer to $4.1 billion and agreed to loan $900 million to Boston Scientific, which would acquire the rest of Guidant. Abbott also is agreeing to buy $1.4 billion worth of Boston Scientific's stock to help that company outbid Johnson & Johnson in the takeover battle for Guidant.

Abbott was not available for comment.

"We believe this issue (J&J's patent claim) has no bearing on our proposed acquisition of Guidant," says a spokesman for Boston Scientific. "Unfortunately, threats of legal action are commonplace in our industry."

Abbott CEO Miles D. White is trying to diversify his product line so it isn't so reliant on drug sales. Abbott sees the Guidant deal as a rare opportunity to quickly become a big player in the market for stents, tiny cylinders used to prop open clogged arteries to the heart and brain. Abbott is developing its own products but would gain those already sold by Indianapolis-based Guidant, in addition to research and a salesforce.

But there are risks involved in getting into a business in which Abbott will play catch-up.

"They're increasing the price and increasing their exposure" to risk, says Ignatius Smetek, president and chief investment officer of Abbott shareholder Arcataur Capital Management LLC in Milwaukee.

For instance, North Chicago-based Abbott would acquire a drug-coated heart stent Guidant is developing. Drug-coated stents are supposed to be effective at keeping arteries from reclogging after heart procedures, and the market for these products may reach $8 billion by 2011, Boston Scientific estimates.

But Abbott, which hopes to have a drug-coated stent on the market by 2008, would enter several years behind New Jersey-based Johnson & Johnson and Massachusetts's Boston Scientific, which already have products on

the market. Medtronic Inc. also is developing a drug-coated stent.

"It will be difficult to significantly penetrate that market," says Mark Morasch, a vascular surgeon and assistant professor at Northwestern University's Feinberg School of Medicine.

Exhibit P

Reuters News

January 20, 2006 Friday 8:35 PM GMT

LENGTH: 411 words

HEADLINE: UPDATE 2-Abbott, Boston shares off on J&J patent threat

DATELINE: January 21, 2006

BODY:

(Adds J&J shares)

CHICAGO, Jan 20 (Reuters) - Shares of Abbott Laboratories Inc. and Boston Scientific Corp. fell on Friday on concerns that Johnson & Johnson <J&J.N> could have patents that might put Boston Scientific's bid for heart device maker Guidant Corp. at risk.

In a research note on Friday, Prudential analyst Larry Biegelsen said J&J claims that two of its patents may be infringed if a company tries to launch a drug-eluting stent coated with a derivative of rapamycin. The drug compound is used to enhance the performance of the stents, or tiny wiremesh tubes.

J&J's Cypher stent is coated with such a compound. So are the experimental stents under development by Abbott and Guidant.

Boston Scientific and Johnson & Johnson are locked in a bidding war over control of Guidant, a maker of heart devices to treat irregular heartbeats and clogged heart arteries.

Guidant's board has said Boston Scientific's offer of $80 per share in cash and stock is superior to a $73 bid by J&J.

Boston Scientific's shares edged down 36 cents, or 1.5 percent, to close at $23.59, while Abbott slid $1.19, or 2.86 percent, at $40.35 amid a broadly weaker market. Shares of J&J also fell $1.37, or 2.2 percent, to $60.80.

"The potential for J&J to prevent Abbott Laboratories and Boston Scientific from marketing (Guidant's Xience-V stent) could give the Guidant board pause," Biegelsen wrote.

"We believe this issue has no bearing on our proposed acquisition of Guidant. Unfortunately, threats of legal action are commonplace in our industry," said Paul Donovan, a spokesman for Boston Scientific.

Abbott spokesman Jonathon Hamilton said the company was undeterred by the report. "We are confident we have freedom to operate," Hamilton said of Abbott's stent. "With respect to Guidant's product, it would be inappropriate for us to comment," he said.

J&J representatives declined to comment.

Many analysts expressed skepticism, saying the concerns over intellectual property were overblown.

One analyst, who asked not to be named, said J&J management was making rounds on Wall Street, trying to fan fears about the Boston Scientific bid.

The analyst said J&J was arguing that Boston Scientific's bid was breaking its bank, that its assumptions on Guidant's cardiac rhythm management were too aggressive and that there was intellectual property infringement that would limit potential of important products. (Additional reporting by Lewis Krauskopf in New York)

NOTES: HEALTH-ABBOTT (UPDATE 2)|LANGEN|ABN|E|RBN|U|M|D|RNP|DNP;
PUBLISHER: Reuters Ltd.

LOAD-DATE: January 21, 2006

Exhibit Q

Medical Device Week

January 24, 2006

ACC-NO: 142590071

LENGTH: 1006 words

HEADLINE: J&J offer rumors persist as Guidant has more ICD issues.

BODY:

J&J offer rumors persist as Guidant has more ICD issues

By HOLLAND JOHNSON

Medical Device Daily Associate Managing Editor

As the bidding war for Guidant (Indianapolis) continued to play itself out as the week began, several new factors were added to an already much-too-complex equation.

Guidant, which already has reported a slew of problems with its pacemakers last year, on Monday reported a new problem with some of itsolder devices. Additionally, rumors began to fly that Johnson & Johnson (J&J; New Brunswick, New Jersey), the original suitor in the escalating bid to acquire Guidant, was poised to make a higher offer for the company.

Guidant said it had identified a second batch of older-model pacemakers that are at risk of malfunction due to a problem with a sealingcomponent. The company recommended physicians reassess their patients due to the discovery of additional devices with the potential defect.

Guidant, which said there have been 145 incidents of malfunction to date related to the seal problem, estimated 16,000 of the affected devices remain implanted in patients worldwide.

This new leak disclosure adds to a previous physician notificationmade this past July (Medical Device Daily, July 19, 2005).

At the time of the first notification, the company said that as ofJuly 11 it had identified 69 devices that may have exhibited this failure, from about 78,000 devices distributed with this component, with about 28,000 devices still implanted worldwide.

It said that no failures were reported for the first 44 months of device use but that "the likelihood of occurrence increases with implant time." Of the 28,000 devices identified and implanted worldwide, 18,000 of them remain in service in the U.S., with an average implantage of 69 months.

As of Jan. 9, a total of five reported incidents out of the secondidentified patient population of 54,000 represented a

rate of occurrence of 0.009%. Guidant said it has confirmed hermetic seal degradation in two of the five reports. It is estimated that 19,300 devices inthis second population remain implanted worldwide.

At the time devices in the second population were assembled, the company said hermetic sealing components susceptible to gradual degradation were mistakenly mixed with a much larger group of non-susceptible components.

The devices in this latest notification were manufactured between Oct. 19, 1998, and Dec. 5, 2000.

Guidant's warranty supplement program, subject to certain conditions, provides a no-cost replacement device and up to $2,500 in unreimbursed medical expenses. The program is available through June 30 and is applicable to both patient populations.

Apparently neither this latest news, nor the documents un-sealed in a Texas court last week that showed that Guidant executives had debated whether to tell doctors about possible heart device malfunctionssix months before the problems were publicly disclosed, has deterredJ&J from making a possible new increased offer for the embattled, but apparently Teflon-coated company.

Rumors began circulating on Monday that J&J would raise its offer,possibly during its quarterly earnings report today, to somewhere inthe neighborhood of $77 to $78 a share - still significantly below rival suitor Boston Scientific's (Natick, Massachusetts) most recent $80 a share bid - but higher than its own initial December 2004 $76-a-share offer.

Fueling this speculation were rumors, some of which apparently were planted by J&J personnel as part of an organized campaign to undermine the Boston Scientific offer in the minds of analysts, that two ofits patents may be infringed if an unnamed company tries to launch adrug-eluting stent coated with a derivative of rapamycin.

J&J's Cypher stent is coated with that compound, as are the experimental stents under development by Guidant and its potential partner in the bidding war for Guidant, Abbott Laboratories (Abbott Park, Illinois). Abbott agreed to contribute $6.4 billion to the Boston Scientific bid and acquire Guidant's vascular business including the new cardiac stent.

Larry Biegelsen, an analyst with Prudential (New York), wrote in aresearch report that "this potential for J&J to prevent Abbott Laboratories and Boston Scientific from marketing [Guidant's] Xience-V DES, could give Guidant's board pause approving a Boston Scientific-Guidant merger."

While Biegelsen said a $78-a-share offer was likely, he noted thatJ&J, with much larger pockets than Boston Scientific, could go as high as $90 a share for Guidant "before an acquisition of St. Jude Medical [St. Paul, Minnesota; another significant player in the cardiac rhythm management space] is more attractive."

"They're trying to tell all of us that there are patents out therethat they have that they feel can stop Boston Scientific," said Jan Wald, an analyst with A.G. Edwards (Boston), in a telephone interviewwith Bloomberg. Wald said he was called by a J&J employee he declined to name.

As part of its recent campaign, J&J also has argued that Boston Scientific's bid was breaking its bank and that its assumptions concerning Guidant's cardiac rhythm management were too aggressive.

While Guidant's board remained silent, Guidant's suitors disputed the rumors floating around Wall Street.

"We believe this issue has no bearing on our proposed acquisition of Guidant. Unfortunately, threats of legal action are commonplace inour industry," Paul Donovan, a spokesman for Boston Scientific, saidin a statement.

Abbott spokesman Jonathon Hamilton said the company was undeterredby the report. "We are confident we have freedom to operate," Hamilton said of Abbott's stent. "With respect to Guidant's product, it would be inappropriate for us to comment."

Guidant said last week that Boston Scientific's offer of $80 a share - $42 in cash and $38 in stock - is "superior" to J&J's current bid of $24.2 billion, or $71 a share, consisting of $40.52 in cash plus0.493 of a J&J share for each Guidant share held (MDD, Jan. 18, 2006). J&J had until today to make a counteroffer.

SOURCE-Medical Device Daily

LOAD-DATE: March 1, 2006

Exhibit R

THE WALL STREET JOURNAL.
The Wall Street Journal

January 26, 2006 Thursday

SECTION: Pg. A1

LENGTH: 1960 words

HEADLINE: Boston Scientific Faces Pivotal Test After Victory in Fight for Guidant

BYLINE: By Thomas M. Burton, Sylvia Pagan Westphal and Dennis K. Berman

BODY:

Boston Scientific Corp., exploiting a monumental case of buyer's remorse by rival Johnson & Johnson, sealed a $27 billion agreement to buy Guidant Corp. in an acquisition that creates a company set on dominating the field of cardiac devices.

The contest between Boston Scientific and J&J gave Wall Street something it hadn't seen in a while -- a large-scale bidding war that ended up putting an extra $6 billion in Guidant investors' pockets.

The deal represents the biggest gamble in the history of Boston Scientific. The Natick, Mass., company has clawed its way into the big time in the health-care business with savvy acquisitions, hardball business tactics and a penchant for navigating threatening regulatory and legal shoals.

The combined company, with revenue of about $9 billion, will have the No. 1 position in the U.S. in selling coronary stents, the tiny arterial implants that now dominate interventional cardiology. It also will have the No. 2 position in selling implantable defibrillators. These increasingly popular products rein in lethally fast heartbeats and have supplanted pacemakers as the main growth area in cardiac electrical therapy. Both products have rich profit margins and stand to benefit from an aging, overweight U.S. population.

Still, to finance the purchase, Boston Scientific will wind up with $11 billion in debt, a burden that has already prompted rating agencies to put it on watch for a possible downgrade. It faces new competitors bringing stents to the market at a time when growth in the overall market has slowed.

Guidant, too, has been losing defibrillator share after recalls because of product malfunctions and ensuing federal investigations and patient lawsuits. Some analysts also see possible difficulties in gaining quick antitrust clearance for the deal.

To help with antitrust clearance, Boston Scientific enlisted help from Abbott Laboratories, another big player in medical devices. Abbott will buy Guidant's stent business and other assets for $4.1 billion, while Boston Scientific will retain shared rights to Guidant stent technology. Abbott will also purchase $1 billion of Boston Scientific stock and lend Boston Scientific $900 million.

Although confident that they can smoothly absorb Guidant and create a powerful health-care company, Boston Scientific executives have been so intensely focused on the bidding competition that celebrating a victorious outcome was nearly forgotten. As Chief Executive Officer James Tobin has put it in various conversations in the past several days, "We're kind of like the dog that caught the bus. Now what are we going to do with the bus?"

J&J sealed a deal to acquire Indianapolis-based Guidant last year. But it provided an opening for Boston Scientific to snatch away its prize when Guidant ran into its recall problems and J&J decided to trim its purchase price to $63 a share from the previously agreed $76. Boston Scientific intervened with its initial offer of $72 a share on Dec. 5.

The bidding war culminated last week, when Guidant's board said Boston Scientific's $80-a-share offer was preferable to a previous $71-a-share offer from J&J. That gave J&J five days to sweeten its $24 billion bid.

During those five days, tension mounted at Boston Scientific, where executives were forced into a waiting game to see what J&J would -- or would not -- do. Mr. Tobin would cut the tension by joking, "It's just a bunch of zeroes. You can't get tight just because it's billions."

They went to bed Tuesday night believing it was very possible that they were going to be aced out once again. No one slept much, especially Chairman Peter Nicholas, who had been traveling across multiple time zones during the bidding war and dealing with resultant jet lag.

Until Boston Scientific's last offer, they had been on the outside looking in, trying to decipher Guidant's true concerns. Each time Guidant chose a lower J&J bid over a higher Boston Scientific one, the Boston executives grew more frustrated as they sought to decipher "incomplete, cryptic information," as one Boston Scientific executive describes it. This was "a major frustration, and it raised the temperature in the room."

Even after Guidant last week declared Boston Scientific's $27.2 billion offer "superior," J&J still had its five-day option. Rumors spread through the executive suites at both Boston Scientific and Guidant: First, that J&J wasn't coming back at all, then, that it was, but at $76 a share, then $78, then $77.50, and finally, a whopping $81 a share, with participation of a third party. According to this rumor, Medtronic Inc. would buy all or part of the Guidant stent business under a J&J deal. Medtronic officials say this didn't happen.

Boston Scientific executives had a meticulous response prepared for each eventuality. "What we weren't prepared for was silence," says one executive on the Boston Scientific side. Boston Scientific executives thought they would hear Tuesday afternoon at 4 p.m., then at 5. Then they were sure they would get definitive documents to sign at 12:02 a.m. yesterday. That didn't happen, and they feared the worst.

At 6:27 a.m. yesterday, an email arrived from Boston Scientific's lawyers, Shearman & Sterling. Boston Scientific had won.

In 4 p.m. New York Stock Exchange composite trading yesterday, Guidant shares fell $1.59, or 2.1%, to $75.19. Boston Scientific shares were down 46 cents, or 1.9%, at $23.54. J&J shares were down 86 cents, or 1.5%, at $58.50.

Boston Scientific was formed in 1979 by John Abele, an inventor who believed in the promise of less-invasive surgery, and Mr. Nicholas, a former Eli Lilly & Co. executive. The purpose of the start-up: buying Medi-Tech Inc., Mr. Abele's employer.

The two scraped together $300,000 and persuaded some Boston bankers to lend them $500,000 more to purchase

Medi-Tech, a maker of catheters, cell-sampling tools and depilatories. In the early days, Boston Scientific grew by using its expertise in catheters to make the tools "larger or shorter, fatter or smaller," depending on how they were to be used, says venture capitalist Thomas Brooks, who joined the company in 1986 when it was still privately held and had fewer than 100 employees.

With a fresh infusion of cash from its 1992 initial public offering, Boston Scientific went on an acquisition binge. The most important purchase was SciMed Life Systems Inc., a successful manufacturer of angioplasty balloons and catheters. Boston Scientific bought it in 1995 for about $850 million in stock.

While that figure pales next to the $27 billion price Boston Scientific will pay for Guidant, the two transactions share one crucial similarity: their ability to catapult Boston Scientific into the top tier of a chosen market. SciMed instantly turned Boston Scientific into one of the leading manufacturers of angioplasty balloons and other products in interventional cardiology. As the likely No. 1 in the market for cardiac devices, Boston Scientific will go head-to-head with current market leader Medtronic.

Driven by Mr. Nicholas, Boston Scientific has bought more than 25 companies in the past 10 years, growing to about 16,000 employees and annual revenue of more than $6 billion. With Guidant, it will acquire 12,000 employees and about $3.6 billion in annual revenue.

The bid for Guidant is being bankrolled, in essence, by Boston Scientific's success in coronary stents. In 2004, Boston Scientific orchestrated one of the most successful product launches in the history of the medical-device industry when it got Food and Drug Administration approval for its Taxus Express drug-coated stent. The drug coating reduces the chance that a buildup of cells around the stent -- called "restenosis" -- will reclog the artery. At the time, J&J was the only company with a drug-coated stent in the U.S.

Boston Scientific made a bold prediction: Taxus would garner 70% of the market in 70 days.

It did better than that, snatching away the lead from J&J and attaining 70% market share within 17 days, according to a company spokesperson. The company posted a 62% revenue increase for 2004, despite a recall of about 99,000 Taxus stents that summer due to malfunctions that caused several injuries and deaths.

The company saw its prospects sour in 2005 as U.S. market share for the stent started to erode -- down to about 54% now -- amid safety concerns about Taxus and a resurgence in popularity for J&J's Cypher. Since their peak in 2004, shares of Boston Scientific are down more than 40%.

Boston Scientific officials believe that Guidant, while damaged by the recall, pending litigation and lost share, will rebound within perhaps a year. The $10 billion business of making defibrillators is growing at a rate of 20% a year. In addition, Guidant's program to produce a stent coated with a drug called everolimus is considered a potentially important one. Guidant's stent is considered easily maneuverable by cardiologists who use it.

Guidant will expose its acquirer to risks of unknown dimension stemming from the company's defibrillator recalls and alleged hiding of problems. Guidant faces a federal investigation by the U.S. Attorney's office in Minneapolis, among other pressures.

Boston Scientific itself fell under a lengthy Justice Department criminal investigation for allegedly shipping stents it knew to be defective. The matter ended last summer in a civil complaint and settlement reached with the U.S. Attorney in Boston. Despite testing that revealed failures at "unacceptably high rates," management at the company decided to continue shipping the stents, the complaint said. In the settlement, Boston Scientific paid $74 million and made no admission of guilt.

Boston Scientific will confront a few hurdles as it subsumes Guidant's products and operations. Among the issues: The deal will give Boston Scientific two drug-coated stents -- its own, which uses the drug paclitaxel, and the

forthcoming everolimus stent.

Some analysts worry that Boston Scientific's proposed arrangement with Abbott Laboratories may not be enough to ward off antitrust concerns. In that case, Boston Scientific may have to distance itself further from the Guidant stent technology, perhaps by selling it entirely.

Complete divestment of Guidant's drug-coated stent technology is "an extremely low likelihood," says Paul Donovan, a spokesman for Boston Scientific. He adds that the company expects the FTC to clear the deal by March 31, with the technology-sharing arrangement.

Another potential wrinkle arises in the intellectual-property rights surrounding stents -- an area that's been the subject of extensive litigation in the industry. Citigroup analyst Matthew Dodds says J&J holds patents on methods of using "limus"-type drugs on stents -- including the everolimus on Guidant's stent, as well as a drug on an Abbott stent.

Now that J&J has lost the battle for Guidant, it isn't likely to license the technology to either Guidant or Abbott, and that could slow down the deal, Mr. Dodds says. "If these patents block a limus, you don't really have" a drug-coated stent program, he says. That would leave only J&J, Boston Scientific and, to a lesser extent, Medtronic, as potential players in the market, a situation that could trouble antitrust reviewers. Mr. Dodds predicts that J&J is "going to make this a big issue with the FTC. . . . They are not incentivized to let them close the deal quickly."

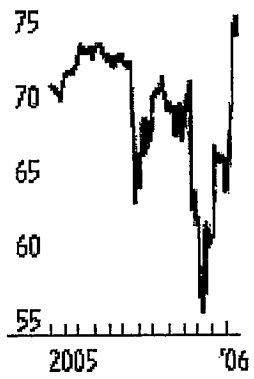
But Boston Scientific's Mr. Donovan says: "We do not consider this to be an issue."

Charles Forelle contributed to this article.

Online Today: WSJ.com subscribers can track Guidant's share price, and see how the company stacks up against Boston Scientific, at WSJ.com/OnlineToday.

Vital Signs

Guidant's stock price:



Source: WSJ Market Data Group

NOTES:
PUBLISHER: Dow Jones & Company, Inc.

LOAD-DATE: January 26, 2006

Exhibit S

DOCKET NO.: CRDS-0005(JJI-51-CON2) **PATENT**
Application No.: 10/951,385

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Carol Wright, et al.

Confirmation No.: **7537**

Application No.: **10/951,385**

Group Art Unit: **3731**

Filing Date: **September 28, 2004**

Examiner:

For: **Local Delivery of Rapamycin for Treatment of Proliferative Sequelae Associated with PTCA Procedures, Including Delivery Using a Modified Stent**

08/09/2006 HDESTA1 00000002 10951385
01 FC:1464 130.00 OP

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT
(37 CFR § 1.102 and MPEP § 708.02)

Applicant hereby petitions to make this application special because of actual infringement.

1. Accompanying material

Accompanying this petition is:

a. A Declaration by Attorney in Support of Petition to Make Special Because of Actual Infringement; and

b. Supplemental Information Disclosure Statement.

2. Fee (37 CFR § 1.17(i))

The fee required is to be paid by:

☒ A check in the amount of **$130.00** is attached.

DOCKET NO.: CRDS-0005(JJI-51-CON2) **PATENT**
Application No.: 10/951,385

☐ Please charge Deposit Account No. 23-3050 in the amount of **$130.00**. This sheet is attached in duplicate.

☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

Date: August 7, 2006

S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

DOCKET NO.: CRDS-0005(JJI-51-CON2) **PATENT**
Application No.: 10/951,385

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Carol Wright, et al.

Confirmation No.: **7537**

Application No.: **10/951,385**

Group Art Unit: **3731**

Filing Date: **September 28, 2004**

Examiner: **Not yet assigned**

For: **Local Delivery of Rapamycin for Treatment of Proliferative Sequelae Associated with PTCA Procedures, Including Delivery Using a Modified Stent**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION BY ATTORNEY IN SUPPORT OF PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT (MPEP § 708.02)

I, S. Maurice Valla, Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia PA, 19103, Registration No. 43,966, Telephone No. 215-564-3100, am the attorney of record for Applicants and make the following declarations.

1. The instant application is directed to drug-eluting stents. Claims 64 to 140 are presently pending. Claims 64 and 103 are the only independent claims. Claim 103 is directed to a device comprising a metallic stent, a biocompatible polymeric carrier and a drug. The drug is rapamycin or a macrocyclic lactone analog thereof and is present in an amount effective to inhibit neointimal proliferation. Claim 130, which depends from claim 103, specifies that the drug is a macrocyclic lactone analog of rapamycin.

2. Attached as exhibits hereto are press releases issued by Guidant Corporation ("Guidant") describing its activities relating to drug eluting stents. In a release dated January 30, 2006 (Exhibit 1), Guidant announced that it has received Conformité Européene (CE) Mark Approval for its XIENCE™ V Everolimus Eluting Coronary Stent System. In the same press release, Guidant states that it "is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE™ V beginning in the second quarter of 2006."

3. In a release dated October 19, 2005 (Exhibit 2), Guidant announced that inspection of its manufacturing facilities in Temecula, California had been successfully concluded as part of its submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. Guidant reported that its European Notified Body found no nonconformities and would recommend certification for Guidant's manufacturing facility for XIENCE™ V.

4. Since Guidant's approved manufacturing facility for XIENCE™ V is in Temecula, California, I conclude that the "ramping up manufacturing and building inventory to . . . support the European launch of XIENCE™ V" to which Guidant's January 30, 2006, release refers is being performed in the United States. Thus, on the basis of these public statements by Guidant, I conclude that Guidant is "making" XIENCE™ V and building inventory in the United States to support launch of the product in Europe.

5. Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

6. I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases, with the claims of the instant application. In my opinion, the XIENCE™ V

product is unquestionably within the scope of at least claims 103 and 130 on file in this application.

7. In a release dated September 21, 2005 (Exhibit 5), Guidant states that XIENCE™ V is being utilized in SPIRIT II and SPIRIT III clinical trials to evaluate the safety and efficacy of the product for the treatment of coronary artery disease. XIENCE™ V is described as "an everolimus eluting coronary stent system utilizing Guidant's cobalt chromium MULTI-LINK VISION® Coronary Stent System platform." In an earlier release, dated April 5, 2004 (Exhibit 6), Guidant stated that it "holds a worldwide exclusive license . . . to use everolimus, a novel proliferation-signal inhibitor with potent anti-proliferative and immunosuppressant properties, in drug eluting stents." The April 5, 2004, release also states that "Guidant has both durable and bioabsorbable polymer drug carriers in development" and that "[t]he company's clinical trials utilizing durable polymer technology are identified by the SPIRIT designation in the study name." In the same press release, the MULTI-LINK VISION® Coronary Stent System is referred to as a "market-leading metallic stent." On the basis of these statements made by Guidant, I conclude that the XIENCE™ V product comprises a metallic stent coated with everolimus and a durable polymer carrier.

8. Everolimus is a macrocyclic lactone analog of rapamycin, bearing a stable 2-hydroxyethyl chain substitution at position 40 on the rapamycin structure (Exhibits 7, 8). In a press release dated March 15, 2006 (Exhibit 9), Guidant stated "everolimus has been shown to reduce tissue proliferation in the coronary vessels following stent implantation." Similarly, in a release dated November 15, 2005 (Exhibit 10), Guidant stated that "[t]he one year data from SPIRIT FIRST continued to demonstrate a preservation of the treatment effect of the XIENCE V Everolimus Eluting Coronary Stent System, with a highly statistically significant reduction of cell proliferation compared to the uncoated control." On the basis of the known structure of everolimus and Guidant's statements, I conclude that the XIENCE™ V product contains a macrocyclic lactone analog of rapamycin in an amount effective to inhibit neointimal proliferation.

9. It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of at least claims 103 and 130 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

10. I have a knowledge of the pertinent prior art by virtue of the prosecution histories of the parents of the instant application and other patents owned by the assignee of the instant application. All such material art is provided to the Examiner as

☒ having been filed

☒ being filed

in a respective Information Disclosure Statement.

10. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: August 7, 2006

S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

Exhibit T

DOCKET NO.: CRDS-0066 **PATENT**
Application No.: Not yet assigned

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Carol Wright, et al.**	Confirmation No.: **Not yet assigned**
Application No.: **Not yet assigned**	Group Art Unit: **Not yet assigned**
Filing Date: **August 24, 2006**	Examiner: **Not yet assigned**

For: **Local Delivery of Rapamycin for Treatment of Proliferative Sequelae Associated with PTCA Procedures, Including Delivery Using a Modified Stent**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT (37 CFR § 1.102 and MPEP § 708.02)

Applicant hereby petitions to make this application special because of actual infringement.

1. Accompanying material

Accompanying this petition is:

A Declaration by Attorney in Support of Petition to Make Special Because of Actual Infringement, with Exhibits 1-9.

2. Fee (37 CFR § 1.17(i))

The fee required is to be paid by:

DOCKET NO.: CRDS-0066 **PATENT**
Application No.: Not yet assigned

☐ A check in the amount of **$130.00** is attached.

☒ Please charge Deposit Account No. 23-3050 in the amount of **$130.00**.

☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

DATE: August 24, 2006

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

DOCKET NO.: CRDS-0066 **PATENT**
Application No.: Not yet assigned

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Carol Wright, et al.**	Confirmation No.:
Application No.: **not yet assigned**	Group Art Unit:
Filing Date: **August 15, 2006**	Examiner: **Not yet assigned**

For: **Local Delivery of Rapamycin for Treatment of Proliferative Sequelae Associated with PTCA Procedures, Including Delivery Using a Modified Stent**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION BY ATTORNEY IN SUPPORT OF PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT (MPEP § 708.02)

I, S. Maurice Valla, Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia PA, 19103, Registration No. 43,966, Telephone No. 215-564-3100, am the attorney of record for Applicants and make the following declarations.

1. The instant application is directed to drug-eluting stents. Claims 1 to 5 are presently pending. Claim 1, the only independent claim, is directed to a metallic stent having a coating applied thereto. The coating comprises a mixture of a polymeric carrier and a therapeutic agent that is rapamycin or a macrocyclic lactone analog thereof and is present in an amount effective to inhibit neointimal proliferation. The device provides a controlled release of the therapeutic agent

over a period of several weeks. Claim 2 recites that the therapeutic agent is a macrocyclic lactone analog of rapamycin, claim 3 recites that the polymeric carrier comprises a fluorinated polymer, and claim 4 recites a polymeric carrier that further comprises an acrylate-based polymer or copolymer. Claim 5 is directed to a method for inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty that comprises implanting a metallic stent according to any one of claims 1 to 4 in the lumen of said coronary artery.

2. Attached as exhibits hereto are several press releases issued by Guidant Corporation ("Guidant") describing its activities relating to drug eluting stents. In a release dated January 30, 2006 (Exhibit 1), Guidant announced that it has received Conformité Européene (CE) Mark Approval for its XIENCE™ V Everolimus Eluting Coronary Stent System. In the same press release, Guidant states that it "is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE™ V beginning in the second quarter of 2006."

3. In a release dated October 19, 2005 (Exhibit 2), Guidant announced that inspection of its manufacturing facilities in Temecula, California had been successfully concluded as part of its submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. Guidant reported that its European Notified Body found no nonconformities and would recommend certification for Guidant's manufacturing facility for XIENCE™ V.

4. Since Guidant's approved manufacturing facility for XIENCE™ V is in Temecula, California, I conclude that the "ramping up manufacturing and building inventory to . . . support the European launch of XIENCE™ V" to which Guidant's January 30, 2006, release refers is being performed in the United States. Thus, on the basis of these public statements by Guidant, I

conclude that Guidant is "making" XIENCE™ V and building inventory in the United States to support launch of the product in Europe.

5. Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

6. I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of claims 1 to 5 on file in this application.

7. Abbott's Fact Sheet attached hereto as Exhibit 4 further states that the XIENCE™ V product elutes everolimus from a MULTI-LINK VISION metallic stent. Everolimus is a macrocyclic lactone analog of rapamycin, bearing a stable 2-hydroxyethyl chain substitution at position 40 on the rapamycin structure (Exhibits 5, 6). In a press release dated March 15, 2006 (Exhibit 7), Guidant stated "everolimus has been shown to reduce tissue proliferation in the coronary vessels following stent implantation." Similarly, in a release dated November 15, 2005 (Exhibit 8), Guidant stated that "[t]he one year data from SPIRIT FIRST continued to demonstrate a preservation of the treatment effect of the XIENCE V Everolimus Eluting Coronary Stent System, with a highly statistically significant reduction of cell proliferation compared to the uncoated control." On the basis of the known structure of everolimus and Guidant's statements, I conclude that the XIENCE™ V product comprises a metallic stent and a macrocyclic lactone analog of rapamycin in an amount effective to inhibit neointimal proliferation.

8. An article published in EuroIntervention in 2005 (Exhibit 9) confirms the XIENCE™ V product comprises a stent bearing a coating that comprises a nonerodible (*i.e.*, nonabsorbable) polymer blended with everolimus (page 59, col. 2). The coating is said to include a blend of acrylic and fluoro polymers, and the article further states that the stent is designed to release approximately 70% of the drug within 30 days after implantation (*Id.*). On the basis of this information, I conclude that the XIENCE™ V product comprises a nonerodible polymeric coating comprising a fluropolymer and an acrylate-based polymer affixed to a metallic stent, and a macrocyclic triene analog of rapamycin incorporated into the coating. I further concluded that the XIENCE™ V product provides a controlled release of the therapeutic agent over a period of several weeks, as recited in claims 1 to 4.

9. The EuroIntervention article cited above (Exhibit 9) further confirms that the XIENCE™ V product is intended for use in a method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty (*see Id.*), as recited in claim 5 of the instant application.

10. It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of claims 1 to 5 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

11. I have a knowledge of the pertinent prior art by virtue of the prosecution histories of the parents of the instant application and other patents owned by the assignee of the instant application. All such material art is provided to the Examiner as

☐ having been filed

☒ being filed

in a respective Information Disclosure Statement.

12. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

DATE: August 24, 2006

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

Exhibit U

DOCKET NO.: CRDS-0067 **PATENT**
Application No.: Not yet assigned

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Carol Wright, et al.**	Confirmation No.: **Not yet assigned**
Application No.: **Not yet assigned**	Group Art Unit: **Not yet assigned**
Filing Date: **August 24, 2006**	Examiner: **Not yet assigned**

For: **Local Delivery of Rapamycin for Treatment of Proliferative Sequelae Associated with PTCA Procedures, Including Delivery Using a Modified Stent**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT (37 CFR § 1.102 and MPEP § 708.02)

Applicant hereby petitions to make this application special because of actual infringement.

1. Accompanying material

   Accompanying this petition is:

   a. A Declaration by Attorney in Support of Petition to Make Special Because of Actual Infringement with Exhibits 1-9.

2. Fee (37 CFR § 1.17(i))

DOCKET NO.: CRDS-0067 **PATENT**
Application No.: Not yet assigned

The fee required is to be paid by:

☐ A check in the amount of **$130.00** is attached.

☒ Please charge Deposit Account No. 23-3050 in the amount of **$130.00**.

☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

DATE: August 24, 2006

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

DOCKET NO.: CRDS-0067 **PATENT**
Application No.: Not yet assigned

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Carol Wright, et al.**	Confirmation No.:
Application No.: **not yet assigned**	Group Art Unit:
Filing Date: **August 15, 2006**	Examiner: **Not yet assigned**

For: **Local Delivery of Rapamycin for Treatment of Proliferative Sequelae Associated with PTCA Procedures, Including Delivery Using a Modified Stent**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION BY ATTORNEY IN SUPPORT OF PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT (MPEP § 708.02)

I, S. Maurice Valla, Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia PA, 19103, Registration No. 43,966, Telephone No. 215-564-3100, am the attorney of record for Applicants and make the following declarations.

1. The instant application is directed to drug-eluting stents. Claims 1 to 5 are presently pending. Claim 1, the only independent claim, is directed to device comprising a metallic stent having a nonabsorbable polymeric carrier, and a therapeutic agent. The polymeric carrier comprises an acrylate-based polymer or copolymer, a fluorinated polymer, or a mixture thereof. The therapeutic agent is rapamycin or a macrocyclic lactone analog thereof and is present in an

amount effective to inhibit neointimal proliferation. Claim 2 recites that the therapeutic agent is a macrocyclic lactone analog of rapamycin, and claims 3 and 4 recite that the device provides a controlled release of the therapeutic agent over a period of several weeks. Claim 5 is directed to a method for inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty that comprises implanting a device according to any one of claims 1 to 4 in the lumen of said coronary artery.

2. Attached as exhibits hereto are several press releases issued by Guidant Corporation ("Guidant") describing its activities relating to drug eluting stents. In a release dated January 30, 2006 (Exhibit 1), Guidant announced that it has received Conformité Européene (CE) Mark Approval for its XIENCE™ V Everolimus Eluting Coronary Stent System. In the same press release, Guidant states that it "is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE™ V beginning in the second quarter of 2006."

3. In a release dated October 19, 2005 (Exhibit 2), Guidant announced that inspection of its manufacturing facilities in Temecula, California had been successfully concluded as part of its submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. Guidant reported that its European Notified Body found no nonconformities and would recommend certification for Guidant's manufacturing facility for XIENCE™ V.

4. Since Guidant's approved manufacturing facility for XIENCE™ V is in Temecula, California, I conclude that the "ramping up manufacturing and building inventory to . . . support the European launch of XIENCE™ V" to which Guidant's January 30, 2006, release refers is being performed in the United States. Thus, on the basis of these public statements by Guidant, I

conclude that Guidant is "making" XIENCE™ V and building inventory in the United States to support launch of the product in Europe.

5. Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

6. I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of claims 1 to 5 on file in this application.

7. Abbott's Fact Sheet attached hereto as Exhibit 4 further states that the XIENCE™ V product elutes everolimus from a MULTI-LINK VISION metallic stent. Everolimus is a macrocyclic lactone analog of rapamycin, bearing a stable 2-hydroxyethyl chain substitution at position 40 on the rapamycin structure (Exhibits 5, 6). In a press release dated March 15, 2006 (Exhibit 7), Guidant stated "everolimus has been shown to reduce tissue proliferation in the coronary vessels following stent implantation." Similarly, in a release dated November 15, 2005 (Exhibit 8), Guidant stated that "[t]he one year data from SPIRIT FIRST continued to demonstrate a preservation of the treatment effect of the XIENCE V Everolimus Eluting Coronary Stent System, with a highly statistically significant reduction of cell proliferation compared to the uncoated control." On the basis of the known structure of everolimus and Guidant's statements, I conclude that the XIENCE™ V product is a device that comprises a metallic stent and a macrocyclic lactone analog of rapamycin in an amount effective to inhibit neointimal proliferation.

8. An article published in EuroIntervention in 2005 (Exhibit 9) confirms the XIENCE™ V product comprises a nonerodible (*i.e.*, nonabsorbable) polymeric carrier that includes a blend of acrylic and fluoro polymers (*Id.*). The article further states that the stent is designed to release approximately 70% of the drug within 30 days after implantation. On the basis of this information, I conclude that the XIENCE™ V product comprises a nonerodible polymeric carrier comprising both a fluropolymer and an acrylate-based polymer, and that it provides a controlled release of the therapeutic agent over a period of several weeks, as recited in claims 1 to 4 of the instant application.

9. The EuroIntervention article cited above (Exhibit 9) further confirms that the XIENCE™ V product is intended for use in a method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty (*see Id.*), as recited in claim 5 of the instant application.

10. It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of claims 1 to 5 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

11. I have a knowledge of the pertinent prior art by virtue of the prosecution histories of the parents of the instant application and other patents owned by the assignee of the instant application. All such material art is provided to the Examiner as

☐ having been filed
☒ being filed

in a respective Information Disclosure Statement.

DOCKET NO.: CRDS-0067 **PATENT**
Application No.: Not yet assigned

12. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

DATE: August 24, 2006

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

Exhibit V

DOCKET NO.: CRDS-0062 (CRD0931CIP) **PATENT**
Application No.: 10/829,074

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Robert Falotico, et al.

Confirmation No.: **5950**

Application No.: **10/829,074**

Group Art Unit: **3743**

Filing Date: **April 21, 2004**

Examiner: **Not yet assigned**

For: **Drug/Drug Delivery Systems for the Prevention and Treatment of Vascular Disease**

08/09/2006 HDESTA1 00000001 10829074
04 FC:1464 130.00 OP

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT
(37 CFR § 1.102 and MPEP § 708.02)

Applicant hereby petitions to make this application special because of actual infringement.

1. Accompanying material

Accompanying this petition is:

a. A Declaration by Attorney in Support of Petition to Make Special Because of Actual Infringement; and

b. Supplemental Information Disclosure Statement.

2. Fee (37 CFR § 1.17(i))

The fee required is to be paid by:

☒ A check in the amount of **$130.00** is attached.

DOCKET NO.: CRDS-0062 (CRD0931CIP) **PATENT**
Application No.: 10/829,074

☐ Please charge Deposit Account No. 23-3050 in the amount of **$130.00**. This sheet is attached in duplicate.

☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

Date: August 7, 2006

S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

DOCKET NO.: CRDS-0062 (CRD0931CIP) **PATENT**
Application No.: 10/829,074

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Robert Falotico, et al.

Confirmation No.: **5950**

Application No.: **10/829,074**

Group Art Unit: **3743**

Filing Date: **April 21, 2004**

Examiner: **Not yet assigned**

For: **Drug/Drug Delivery Systems for the Prevention and Treatment of Vascular Disease**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION BY ATTORNEY IN SUPPORT OF PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT (MPEP § 708.02)

I, S. Maurice Valla, Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia PA, 19103, Registration No. 43,966, Telephone No. 215-564-3100, am the attorney of record for Applicants and make the following declarations.

1. Claims 15 to 30 are presently pending. Each of the claims is directed to devices comprising an intraluminal stent, a nonerodible polymeric coating affixed to the stent, and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the coating; the devices provide an in-stent late loss in diameter at 12 months following implantation in a human of less than about 0.5 mm, as measured by quantitative coronary angiography. Claim 16 specifies an in-stent late loss in diameter of less than about 0.3 mm, and claims 17 and 18 specify that the stent provides an in-stent diameter stenosis at 12 months following implantation in a human of less than about 22% or 15%, respectively, as

measured by quantitative coronary angiography. Claims 19 to 22 are similar to claims 15 to 18, but specify mean in-stent late loss and in-stent diameter stenosis values for in a human population. Claims 23 to 30 are directed to methods of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty, comprising implanting in the lumen of said coronary artery a drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating. These methods provide in-stent late loss and/or in-stent diameter stenosis values as recited in claims 15 to 22.

2. Attached as exhibits hereto are press releases issued by Guidant Corporation ("Guidant") describing certain of its activities relating to drug eluting stents. In a release dated January 30, 2006 (Exhibit 1), Guidant announced that it has received Conformité Européene (CE) Mark Approval for its XIENCE™ V Everolimus Eluting Coronary Stent System. In the same press release, Guidant states that it "is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE™ V beginning in the second quarter of 2006."

3. In a release dated October 19, 2005 (Exhibit 2), Guidant announced that inspection of its manufacturing facilities in Temecula, California had been successfully concluded as part of its submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. Guidant reported that its European Notified Body found no nonconformities and would recommend certification for Guidant's manufacturing facility for XIENCE™ V.

4. Since Guidant's approved manufacturing facility for XIENCE™ V is in Temecula, California, I conclude that the "ramping up manufacturing and building inventory to . . . support the European launch of XIENCE™ V" to which Guidant's January 30, 2006, release refers is being performed in the United States. Thus, on the basis of these public statements by Guidant, I conclude that Guidant is "making" XIENCE™ V and building inventory in the United States to support launch of the product in Europe.

5. Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

6. I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases and other publicly available documents, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of claims 15 to 30 on file in this application.

7. Everolimus is a macrocyclic triene analog of rapamycin, bearing a stable 2-hydroxyethyl chain substitution at position 40 on the rapamycin structure (Exhibits 5,6). An article published in EuroIntervention in 2005 (Exhibit 7) confirms that everolimus binds with FKBP12 (*see* page 59, col. 1), and that XIENCE™ V product comprises a stent bearing a coating that comprises a nonerodible polymer blended with everolimus (*see* page 59, col. 2). On the basis of this information, I conclude that the XIENCE™ V product comprises an intraluminal stent, a nonerodible polymeric coating affixed to the stent, and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the coating, as recited in claims 15 to 30 on file in this application.

8. Another article published in EuroIntervention in 2005 (Exhibit 8) reports on one-year results from Guidant's SPIRIT FIRST clinical trial, in which intravascular ultrasound and quantitative angiographic analyses were performed one year following intraluminal implantation of XIENCE™ V stents in the coronary arteries of human patients. The article reports that mean in-stent late loss and diameter stenosis values were 0.24mm and 18%, respectively (*see* abstract), which is within the limits recited in claims 15 to 30 on file in this application.

9. It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of claims 15 to 30 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

10. I have a knowledge of the pertinent prior art by virtue of the prosecution histories of the parents of the instant application and other patents owned by the assignee of the instant application. All such material art is provided to the Examiner as

☒ having been filed

☒ being filed

in a respective Information Disclosure Statement.

11. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

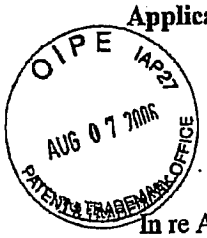
Date: August 7, 2006

S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

Exhibit W

DOCKET NO.: CRDS-0064 (CRD0932CIP) **PATENT**
Application No.: 10/852,517



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Robert Falotico, et al.

Confirmation No.: **4554**

Application No.: **10/852,517**

Group Art Unit: **3743**

Filing Date: **May 24, 2004**

Examiner: **Not yet assigned**

For: **ANTIPROLIFERATIVE DRUG AND DELIVERY DEVICE**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT
(37 CFR § 1.102 and MPEP § 708.02)

Applicant hereby petitions to make this application special because of actual infringement.

1. Accompanying material

   Accompanying this petition is:

   a. A Declaration by Attorney in Support of Petition to Make Special Because of Actual Infringement; and

   b. Supplemental Information Disclosure Statement.

2. Fee (37 CFR § 1.17(i))

   The fee required is to be paid by:

   ☒ A check in the amount of **$130.00** is attached.

DOCKET NO.: CRDS-0064 (CRD0932CIP) **PATENT**
Application No.: 10/852,517

☐ Please charge Deposit Account No. 23-3050 in the amount of **$130.00**. This sheet is attached in duplicate.

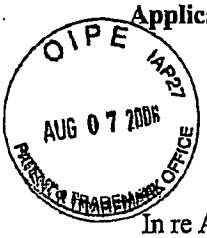
☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

Date: August 7, 2006

S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

DOCKET NO.: CRDS-0064 (CRD0932CIP) **PATENT**
Application No.: 10/852,517



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Robert Falotico, et al.

Confirmation No.: **4554**

Application No.: **10/853,517**

Group Art Unit: **3743**

Filing Date: **May 24, 2004**

Examiner: **Not yet assigned**

For: **ANTIPROLIFERATIVE DRUG AND DELIVERY DEVICE**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION BY ATTORNEY IN SUPPORT OF PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT (MPEP § 708.02)

I, S. Maurice Valla, Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia PA, 19103, Registration No. 43,966, Telephone No. 215-564-3100, am the attorney of record for Applicants and make the following declarations.

1. Claims 5 to 9 are presently pending. These claims are directed to drug delivery devices and methods of using same. The devices comprise: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and a therapeutic dosage of a macrocyclic triene analog of rapamycin that binds FKBP12 and is incorporated into the polymeric coating; a portion of the therapeutic dosage is released during a period of about two weeks to about six weeks following intraluminal implantation. Claim 8 is directed to methods of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting the claimed drug delivery device in the lumen of said coronary artery. Claim 9, which depends from

claim 8, is directed to methods of this type that provide a reduction in in-stent neointimal hyperplasia that is present for at least one year following intraluminal implantation of the device.

2. Attached as exhibits hereto are press releases issued by Guidant Corporation ("Guidant") describing certain of its activities relating to drug eluting stents. In a release dated January 30, 2006 (Exhibit 1), Guidant announced that it received Conformité Européene (CE) Mark Approval for its XIENCE™ V Everolimus Eluting Coronary Stent System. In the same press release, Guidant states that it "is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE™ V beginning in the second quarter of 2006" (*Id.*).

3. In a release dated October 19, 2005 (Exhibit 2), Guidant announced that inspection of its manufacturing facilities in Temecula, California had been successfully concluded as part of its submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. Guidant reported that its European Notified Body found no nonconformities and would recommend certification for Guidant's manufacturing facility for XIENCE™ V (*Id.*).

4. Because Guidant announced that its approved manufacturing facility for the XIENCE™ V product is in Temecula, California, I conclude that the "ramping up manufacturing and building inventory to . . . support the European launch of XIENCE™ V" to which Guidant's January 30, 2006, release refers is being performed in the United States. Thus, on the basis of these public statements by Guidant, I conclude that Guidant is "making" the XIENCE™ V product and building inventory in the United States to support launch of the product in Europe.

5. Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch the XIENCE™ V product in Europe in the third quarter of 2006 (Exhibit 4).

6. I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases and other publicly available documents, with the claims of the instant

application. In my opinion, the XIENCE™ V product is unquestionably within the scope of claims 4, 7 and 8 on file in this application.

7. Everolimus is a macrocyclic triene analog of rapamycin, bearing a stable 2-hydroxyethyl chain substitution at position 40 on the rapamycin structure (Exhibits 5, 6). An article published in EuroIntervention in 2005 (Exhibit 7) confirms that everolimus binds with FKBP12 (page 59, col. 1), and that the XIENCE™ V product comprises a stent bearing a coating that comprises a nonerodible polymer blended with everolimus (page 59, col. 2). The article further states that the stent is designed to release approximately 70% of the drug within 30 days after implantation (*Id.*). On the basis of this information, I conclude that the XIENCE™ V product comprises an intraluminal stent, a nonerodible polymeric coating affixed to the stent, and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the coating, and releases a portion of the drug during a period of about two weeks to about six weeks, as recited claims on file in this patent application.

8. Another EuroIntervention article (Exhibit 8) reports on one-year results from Guidant's SPIRIT FIRST clinical trial, in which intravascular ultrasound and quantitative angiographic analyses were performed one year following intraluminal implantation of XIENCE™ V stents in the coronary arteries of human patients. The article reports that the stents provide reductions in in-stent late loss and diameter stenosis, two frequently cited indicators of neointimal hyperplasia, that is present at one year following implantation (*see* abstract), as recited in claim 8 of this patent application.

9. It is therefore my opinion that the product Guidant in the United States to support the European launch is unquestionably within the scope of at least claims 5, 8 and 9 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

10. I have a knowledge of the pertinent prior art by virtue of the prosecution histories of the parents of the instant application and other patents owned by the assignee of the instant application. All such material art is provided to the Examiner as

☒ having been filed

☒ being filed

in a respective Information Disclosure Statement.

11. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: August 7, 2006

S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

Exhibit X

DOCKET NO.: CRDS-0068 **PATENT**
Application No.: Not yet assigned

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Robert Falotico, et al.**	Confirmation No.: **Not yet assigned**
Application No.: **Not yet assigned**	Group Art Unit: **Not yet assigned**
Filing Date: **August 24, 2006**	Examiner: **Not yet assigned**

For: **Drug/Drug Delivery Systems for the Prevention and Treatment of Vascular Disease**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT
(37 CFR § 1.102 and MPEP § 708.02)

Applicant hereby petitions to make this application special because of actual infringement.

1. Accompanying material

   Accompanying this petition is:

   a. A Declaration by Attorney in Support of Petition to Make Special Because of Actual Infringement with Exhibits 1-8.

2. Fee (37 CFR § 1.17(i))

   The fee required is to be paid by:

   ☐ A check in the amount of **$130.00** is attached.

DOCKET NO.: CRDS-0068 **PATENT**
Application No.: Not yet assigned

☒ Please charge Deposit Account No. 23-3050 in the amount of **$130.00**.

☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

DATE: August 24, 2006

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

DOCKET NO.: CRDS-0068 **PATENT**
Application No.: Not yet assigned

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Robert Falotico, et al.**	Confirmation No.: **Not yet assigned**
Application No.: **Not yet assigned**	Group Art Unit: **Not yet assigned**
Filing Date: **August 24, 2006**	Examiner: **Not yet assigned**

For: **Drug/Drug Delivery Systems for the Prevention and Treatment of Vascular Disease**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION BY ATTORNEY IN SUPPORT OF PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT (MPEP § 708.02)

I, S. Maurice Valla, Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia PA, 19103, Registration No. 43,966, Telephone No. 215-564-3100, am the attorney of record for Applicants and make the following declarations.

1. Claims 1 to 14 are presently pending. Claim 1 is directed to a drug delivery device comprising an intraluminal stent, a nonerodible polymeric coating affixed to the stent, and a dose of from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating. The claim further recites that the device releases a portion of the dose on any of days three to about fifty-six following intraluminal implantation. Independent claim 8 is similar to claim 1, but recites that the rapamycin or macrocyclic triene analog thereof is present at a dose of from about 2 μg to about 30 μg per millimeter of stent length. Dependent claims 3 and 10 specify that the devices release a portion

of the dose during a period of about two weeks to about six weeks following intraluminal implantation. Claim 5 recites a device according to claim 1 or 3 that contains from about 64 μg to about 125 μg of the drug. Claim 12 recites a device according to claim 8 or 10 wherein the rapamycin or macrocyclic triene analog thereof is present at a dose of from about 3 μg to about 13 μg per millimeter of stent length. Claims 6, 7, 13 and 14 are directed to methods of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting a drug delivery device as defined above in the lumen of said coronary artery.

2. Attached as exhibits hereto are press releases issued by Guidant Corporation ("Guidant") describing certain of its activities relating to drug eluting stents. In a release dated January 30, 2006 (Exhibit 1), Guidant announced that it has received Conformité Européene (CE) Mark Approval for its XIENCE™ V Everolimus Eluting Coronary Stent System. In the same press release, Guidant states that it "is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE™ V beginning in the second quarter of 2006."

3. In a release dated October 19, 2005 (Exhibit 2), Guidant announced that inspection of its manufacturing facilities in Temecula, California had been successfully concluded as part of its submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. Guidant reported that its European Notified Body found no nonconformities and would recommend certification for Guidant's manufacturing facility for XIENCE™ V.

4. Since Guidant's approved manufacturing facility for XIENCE™ V is in Temecula, California, I conclude that the "ramping up manufacturing and building inventory to . . . support the European launch of XIENCE™ V" to which Guidant's January 30, 2006, release refers is being performed in the United States. Thus, on the basis of these public statements by Guidant, I conclude that Guidant is "making" XIENCE™ V and building inventory in the United States to support launch of the product in Europe.

5. Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

6. I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases and other publicly available documents, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of at least claims 1, 3, 5, 6 to 8, 10, and 12 to 14 on file in this application.

7. Everolimus is a macrocyclic triene analog of rapamycin, bearing a stable 2-hydroxyethyl chain substitution at position 40 on the rapamycin structure (Exhibits 5,6). An article published in EuroIntervention in 2005 (Exhibit 7) confirms that everolimus binds with FKBP12 (*see* page 59, col. 1), and that the XIENCE™ V product is intended for use in method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty (*see e.g.*, page 59, col. 1). This article further confirms that XIENCE™ V product comprises a MULTI-LINK VISION® stent bearing a coating that comprises a nonerodible polymer blended with everolimus at a dose of 100 μg per cm^2 (*see* page 59, col. 2). On the basis of this information, I conclude that the XIENCE™ V product comprises an intraluminal stent, a nonerodible polymeric coating affixed to the stent, and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the coating at a dose of 100 μg per cm^2.

8. Attached hereto is the Declaration of Ramesh V. Marrey, Ph.D., an engineer at Cordis Corporation with considerable familiarity with intraluminal stents (Exhibit 8). Dr. Marrey performed surface area measurements on two MULTI-LINK VISION® stents of a size (*i.e.*, 3.0 mm X 18 mm) that is commonly used in percutaneous transluminal coronary angioplasty (*Id.*, ¶2). From these measurements, Dr. Marrey calculates the surface area of this size MULTI-LINK VISION® stent to be approximately 0.92 cm^2 (*Id.*, ¶8). Since the XIENCE™ V product is a MULTI-LINK VISION® stent that is said to bear a coating comprising 100 μg per cm^2 of everolimus, each 3.0 mm X 18 mm XIENCE™ V product would be expected to include approximately 92 μg total of everolimus (*i.e.*, 100 μg per cm^2 multiplied by 0.92 cm^2), or approximately 5.1 μg of everolimus per millimeter of stent length.

9. It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of at least claims 1, 3, 5, 6 to 8, 10, and 12 to 14 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

10. I have a knowledge of the pertinent prior art by virtue of the prosecution histories of the parents of the instant application and other patents owned by the assignee of the instant application. All such material art is provided to the Examiner as

☐ having been filed

☒ being filed

in a respective Information Disclosure Statement.

11. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATE: August 24, 2006

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

Exhibit Y

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

JUDGE LYNCH

06 CV 7685

JOHNSON & JOHNSON, a New Jersey Corporation,

Plaintiffs,

- against -

GUIDANT CORPORATION, an Indiana Corporation, BOSTON SCIENTIFIC CORPORATION, a Delaware Corporation, and ABBOTT LABORATORIES, an Illinois Corporation,

Defendants.

Civil Action No. ____

Complaint

Johnson & Johnson ("J&J"), by its attorneys, Kramer Levin Naftalis & Frankel LLP, for its complaint against Guidant Corporation ("Guidant"), Boston Scientific Corporation ("Boston Scientific") and Abbott Laboratories ("Abbott"), alleges as follows:

I. Nature of the Action

1. This action arises out of the highly publicized takeover battle between J&J and Boston Scientific to acquire Guidant. While Boston Scientific ultimately succeeded in its takeover bid for Guidant, it did so only because Guidant leaked confidential information to a third party, Abbott, for the purpose of arranging a prepackaged divestiture of significant Guidant businesses to Abbott. Based on these disclosures, which were in material breach of the terms of Guidant's merger agreement with J&J, Abbott agreed to enter into a divestiture and financing agreement with Boston Scientific, which allowed Boston Scientific to make an offer for Guidant that would not require a lengthy and uncertain antitrust review. This, in turn, allowed Guidant to accept Boston Scientific's offer as "superior" to J&J's offer and to terminate the agreement with

J&J. Thus, Guidant's breach of its agreement with J&J, and Boston Scientific's and Abbott's tortious interference with that agreement, deprived J&J of the benefit of the bargain of its merger with Guidant and caused it to suffer damages.

2. In December 2004, J&J and Guidant entered into a merger agreement that provided that J&J would pay $25.4 billion to acquire Guidant, or $76 per Guidant share (the "Initial Merger Agreement"). Guidant's shareholders approved the merger. The price was subsequently changed to $21.5 billion, or $63.08 per share, as a result of various product recalls and legal problems that surfaced at Guidant. In this regard, the parties entered into an Amended and Restated Agreement and Plan of Merger dated November 14, 2005 (the "Merger Agreement").

3. Like any large multi-national acquisition, the merger was subject to antitrust approval by U.S., European Union and other foreign regulators. Over the following ten months, J&J reached an agreement with domestic and foreign regulators which, among other things, would grant a non-exclusive license for certain patents to Abbott to facilitate antitrust approval for the merger with Guidant.

4. Pending the closing of the merger, Guidant was prohibited under the express terms of the Merger Agreement from soliciting alternative offers and had limited ability to respond to an unsolicited bid from another party. Under the "No Solicitation" provision in the Merger Agreement — which was designed to prevent Guidant from using the Merger Agreement to solicit higher offers — Guidant was prohibited from providing confidential business information to any company, or its representatives, unless that company was making an unsolicited "Takeover Proposal" (*i.e.*, a proposal to acquire 15% or more of Guidant) under

terms that were likely to result in a bid that constituted a "Superior Proposal" to the merger with J&J. Guidant also could not facilitate or cooperate with a Takeover Proposal other than through discussions with, and disclosures to, the person making such a Takeover Proposal. Under no circumstances could Guidant provide confidential business information to or discuss or negotiate with any third party that was not making a bona fide Takeover Proposal.

5. In December 2005, just as the J&J/Guidant merger was about to close, Boston Scientific made a bid to acquire Guidant for $25 billion, or $72 per Guidant share. While nominally higher in price than the renegotiated deal with J&J, Boston Scientific's offer was fraught with uncertainty and timing issues that rendered its proposal patently inferior to the merger with J&J. For example, unlike J&J, which had spent much of the past year resolving potential antitrust issues by entering into a License Agreement with Abbott and a Consent Decree with the regulators, Boston Scientific had not even begun the pre-merger notification process, much less resolved its own antitrust issues, at the time of its announced bid.

6. After receiving a Takeover Proposal from Boston Scientific, Guidant's management allowed Boston Scientific to perform limited due diligence. What Guidant did not disclose until after the fact, however, was that it simultaneously allowed Abbott — a third party with absolutely no right to receive any confidential information from Guidant under the No Solicitation provision and which had already agreed to facilitate J&J's bid — an even "deeper dive" into Guidant's confidential business information to determine whether Abbott would now be willing to enter into a pre-packaged divestiture agreement with Boston Scientific to clear any antitrust hurdles. In so doing, Guidant materially breached the No Solicitation provision of its Merger Agreement with J&J.

7. Based on the information disclosed to it by Guidant, Abbott and Boston Scientific entered into an agreement to divest Guidant's entire vascular intervention ("VI") business and other assets and Boston Scientific then made a formal proposal to acquire Guidant for $72 per share. On January 25, 2006, after several counter-proposals from J&J and Boston Scientific, Guidant announced that it was terminating the Merger Agreement with J&J and entering into an acquisition agreement with Boston Scientific for $27 billion.

8. Abbott would not have agreed to a pre-packaged divestiture without the confidential information it received in violation of the "No–Solicitation" provision of J&J's Merger Agreement with Guidant. Without a pre-packaged divestiture agreement, Boston Scientific could not have made a proposal that would have been acceptable to Guidant's Board of Directors or shareholders, both because it would have been conditioned on reaching an agreement with Abbott or some other party to resolve antitrust issues and would have entailed a lengthy antitrust review, the outcome of which would have been uncertain.

9. Guidant could have terminated its Merger Agreement with J&J and then provided information to Abbott, but would then have lost the ability to keep J&J bound to a deal if a transaction with Boston Scientific failed to materialize. Guidant was also able to use its agreement with J&J to better its negotiating position with Boston Scientific. By keeping J&J contractually bound while it facilitated what was ultimately declared a Superior Proposal from Boston Scientific, Guidant acted in bad faith and in violation of its contractual restrictions pending the closing of the Merger Agreement with J&J.

10. Boston Scientific and Abbott were well aware that Guidant had entered into the Merger Agreement with J&J; indeed, Abbott had agreed to facilitate consummation of

that transaction before it began dealing with Boston Scientific behind J&J's back. By their actions, these defendants induced Guidant to breach that agreement by disclosing confidential information to Abbott with the goal of ensuring the success of Boston Scientific's Takeover Proposal.

11. As a result of Guidant's willful and material breach, and the tortious interference by Boston Scientific and Abbott, J&J was deprived of the benefit of its merger agreement and suffered damages that it now seeks to recover through this action.

II. Jurisdiction and Venue

12. The Court has diversity jurisdiction over the subject matter of this case, under 28 U.S.C. § 1332, because this case arises among citizens of different states and the amount in controversy exceeds the sum or value of $75,000.

13. The Court has jurisdiction over the parties, each of which is a corporation doing business in the State of New York, and jurisdiction to grant all the relief requested by J&J.

14. Venue is proper in the Southern District of New York because one party, Guidant, is subject to and has consented to the jurisdiction of this Court and there is no other district in which this action may otherwise be brought.

III. The Parties

15. J&J is a New Jersey corporation with its headquarters and principal place of business at One Johnson & Johnson Plaza, New Brunswick, New Jersey. Through its operating subsidiaries, J&J is a multi-national manufacturer and distributor of health care, surgical, biotechnology, and personal hygiene products, as well as a provider of related services

for the consumer, pharmaceutical, medical devices, and diagnostics markets. J&J has more than 230 operating companies, which employ approximately 116,000 people in 57 countries and sell products in the United States and around the world.

16. Guidant is an Indiana corporation having a principal place of business at 11 Monument Circle, Indianapolis, Indiana. It is now a wholly-owned subsidiary of Boston Scientific. Guidant designs, develops, and markets cardiovascular medical products, including pacemakers and implantable defibrillators.

17. Boston Scientific is a Delaware corporation having a principal place of business at One Boston Scientific Place, Natick, Massachusetts. Boston Scientific develops, manufactures and markets a range of medical devices and procedures.

18. Abbott is an Illinois corporation having a principal place of business at 100 Abbott Park Road, Abbott Park, Illinois. Abbott develops, manufactures, and markets pharmaceutical and nutritional products, as well as surgical and diagnostic devices.

IV. Background Facts

(a) J&J and Guidant Engage in Confidential Merger Discussions

19. Among other products, J&J, through its subsidiary Cordis Corporation ("Cordis"), markets medical devices for the treatment of cardiovascular disorders, including a coronary stent known as the Cypher stent. A stent is a metallic device surgically inserted to keep arteries open after balloon angioplasty to clear blockages. The Cypher stent provides a mechanical scaffold to keep the vessel open while a drug is slowly released from the stent to

prevent the build-up of new tissue that re-clogs the artery. Stents that work with drugs like this are known in the industry as drug-eluting stents ("DES").

20. DES account for over 80% of the U.S. coronary stent market. Aside from Cordis, Boston Scientific is the only other company that markets DES in the U.S., with Cordis having approximately a 45% market share and Boston Scientific approximately a 55% market share. Guidant, Abbott and another company called Medtronic are all in the process of seeking, or undertaking the preparations necessary to seek, approval of the Food and Drug Administration to market DES in this country.

21. During the fall 2004, J&J engaged in discussions with Guidant about the possibility of entering into a business transaction whereby J&J would acquire Guidant. The acquisition of Guidant represented an opportunity for J&J to expand its business into the cardiac rhythm management market for implantable pacemakers and defibrillators.

22. On or about August 4, 2004, J&J and Guidant entered into a Confidentiality Agreement that provided that information exchanged between J&J and Guidant would be used solely for the purpose of exploring a possible negotiated business arrangement and not for any other business or competitive purpose.

(b) J&J and Guidant Enter into a Merger Agreement

23. On December 15, 2004, J&J and Guidant entered into the Initial Merger Agreement pursuant to which J&J agreed to pay $25.4 billion in cash and stock or $76 per share to acquire Guidant. The closing of the merger was conditioned on (i) approval of the deal by Guidant shareholders, (ii) approval for listing on the New York Stock Exchange of newly registered J&J stock for issuance to Guidant shareholders, (iii) regulatory approval of the

transaction, including any divestitures, from U.S. and European Commission antitrust authorities, and (iv) the accuracy of the representations and warranties set forth in the agreement.

24. With Guidant's assistance, J&J prepared and filed with the Securities and Exchange Commission a Registration Statement on Form S-4 in connection with the issuance of J&J stock in the merger, as well as a Proxy Statement for the Merger that was included as a Prospectus.

25. Guidant gave notice of, convened, and held a meeting of its shareholders solely for the purpose of obtaining shareholder approval of the merger. On or about April 27, 2005, Guidant shareholders approved the merger.

26. J&J also sought the necessary antitrust clearance for the merger in the United States, Europe, and Canada. To this end, J&J filed a pre-merger notification under the Hart-Scott-Rodino Antitrust Act of 1976 with the Federal Trade Commission ("FTC") on January 18, 2005.

27. In discussions with the FTC, the agency objected to the proposed transaction on the ground that a merger between one of two actual competitors in the DES market with one of the three potential competitors would lessen competition in that market. On August 12, 2005, J&J and Abbott entered into a License Agreement whereby J&J granted Abbott a non-exclusive license to certain patents in the DES field in the event the transaction was consummated in order to increase the likelihood that Abbott would successfully enter the DES market. After lengthy negotiations, and based in part on the agreement between J&J and Abbott, the FTC and J&J entered into a Consent Order on November 2, 2005 to resolve the FTC's antitrust concerns.

28. In the meantime, numerous regulatory and legal problems surfaced involving Guidant products being recalled, lawsuits against Guidant being filed, and Guidant being investigated by the New York Attorney General. On October 18, 2005, J&J announced that the company was considering alternatives to its proposed acquisition of Guidant and on November 7, Guidant sued J&J claiming a breach of the Initial Merger Agreement. On November 14, Guidant accepted a revised offer of $21.5 billion, or $63.08 per Guidant share, the Merger Agreement was executed and the lawsuit was discontinued.

(c) The Merger Agreement Contained Strict Limitations on Guidant's Ability to Solicit or Cooperate with Competing Bids, Designed to Protect the Benefit of J&J's Bargain

29. Pursuant to the Merger Agreement, Guidant was prohibited from either (i) soliciting, initiating or knowingly encouraging, or taking any other action designed to, or which could reasonably be expected to, facilitate, any competing proposal to acquire Guidant or (ii) entering into, continuing or otherwise participating in any discussions or negotiations regarding, or furnishing to any person any information, or otherwise cooperating with any such proposal. These restrictions were designed to prevent Guidant from using the J&J offer as a means of obtaining higher bids for the company.

30. In particular, Section 4.02 of the Merger Agreement, titled "No Solicitation," provided as follows:

> The Company [*i.e.*, Guidant] shall not, nor shall it authorize or permit any of its Subsidiaries or any of their respective directors, officers or employees or any investment banker, financial advisor, attorney, accountant or other advisor, agent or representative (collectively, "Representatives") retained by it or any of its Subsidiaries to, directly or indirectly through another person, *(i) solicit, initiate or knowingly encourage, or take any other action designed to, or which could reasonably be expected to, facilitate, any Takeover Proposal or (ii) enter into, continue or otherwise*

> *participate in any discussions or negotiations regarding, or furnish to any person any information, or otherwise cooperate in any way with, any Takeover Proposal.* (Emphasis added).

31. Section 4.02 of the Merger Agreement defined a "Takeover Proposal" as basically a bid for at least 15% of Guidant's assets or businesses:

> The term "Takeover Proposal" means any inquiry, proposal or offer from any person relating to, or that could reasonably be expected to lead to, any direct or indirect acquisition or purchase, in one transaction or a series of transactions, of assets (including equity securities of any Subsidiary of the Company) or businesses that constitute 15% or more of the revenues, net income or assets of the Company and its Subsidiaries, taken as a whole, or 15% or more of any class of equity securities of the Company, any tender offer or exchange offer that if consummated would result in any person beneficially owning 15% or more of any class of equity securities of the Company, or any merger, consolidation, business combination, recapitalization, liquidation, dissolution, joint venture, binding share exchange or similar transaction involving the Company or any of its Subsidiaries pursuant to which any person or the shareholders of any person would own 15% or more of any class of equity securities of the Company or of any resulting parent company of the Company, in each case other than the transactions contemplated by this Agreement.

32. Notwithstanding these provisions, and in order to allow Guidant's directors to meet their fiduciary obligations to Guidant's shareholders, the Merger Agreement provided that if Guidant's Board of Directors, in consultation with outside legal counsel and a qualified financial advisor, determined that an unsolicited Takeover Proposal constituted or was reasonably likely to lead to a "Superior Proposal," as defined below, then, and only then, Guidant could (i) provide information to the "person making such Takeover Proposal (and its Representatives)," pursuant to an appropriate confidentiality agreement and as long as Guidant simultaneously provided (or already had provided) the information to J&J, and/or (ii) "participate in discussions or negotiations with the person making such Takeover Proposal (and its Representatives)."

33. In this regard, Section 4.02 provided as follows:

> Notwithstanding the foregoing, at any time prior to obtaining the Shareholder Approval, in response to a bona fide written Takeover Proposal that the Board of Directors of the Company reasonably determines (after consultation with outside counsel and a financial advisor of nationally recognized reputation) constitutes or is reasonably likely to lead to a Superior Proposal, and which Takeover Proposal was not solicited after the date hereof and was made after the date hereof and did not otherwise result from a breach of this Section 4.02(a), the Company may, subject to compliance with Section 4.02(c), (x) furnish information with respect to the Company and its Subsidiaries to the person making such Takeover Proposal (and its Representatives) pursuant to a customary confidentiality agreement not less restrictive to such person than the confidentiality provisions of the Confidentiality Agreement, *provided* that all such information has previously been provided to Parent or is provided to Parent prior to or substantially concurrent with the time it is provided to such person, and (y) participate in discussions or negotiations with the person making such Takeover Proposal (and its Representatives) regarding such Takeover Proposal.

34. As further defined in Section 4.02, "Representatives" of a person making a Takeover Proposal included only that person's "Subsidiaries or any of their respective directors, officers or employees or any investment banker, financial advisor, attorney, accountant or other advisor, agent or representative (collectively, 'Representatives')." Guidant was expressly prohibited from giving information to, or participating in discussions with, any other persons.

35. Whether a Takeover Proposal constituted or likely would lead to a Superior Proposal was to be based not only on its financial terms, but also on whether it was "reasonably capable of being completed, taking into account all financial, legal, regulatory and other aspects of such proposal." Thus, under Section 4.02:

> The term "Superior Proposal" means any bona fide offer made by a third party that if consummated would result in such person (or its shareholders) owning, directly or indirectly, more than 80% of

> the shares of Company Common Stock then outstanding (or of the shares of the surviving entity in a merger or the direct or indirect parent of the surviving entity in a merger) or all or substantially all the assets of the Company, which the Board of Directors of the Company reasonably determines (after consultation with a financial advisor of nationally recognized reputation) to be (i) more favorable to the shareholders of the Company from a financial point of view than the Merger (taking into account all the terms and conditions of such proposal and this Agreement (including any changes to the financial terms of this Agreement proposed by Parent in response to such offer or otherwise)) and (ii) *reasonably capable of being completed, taking into account all financial, legal, regulatory and other aspects of such proposal.* [Emphasis added]

36. In sum, under the Merger Agreement, Guidant could not solicit any Takeover Proposal from another person. In the event that it received an unsolicited Takeover Proposal, which it determined upon consultation with its legal and financial advisors was or could become a Superior Proposal, Guidant could furnish information to, and conduct discussions with, only the person (or its Representatives) making such a Takeover Proposal.

37. The Merger Agreement also provided that in the event Guidant's Board received a Superior Offer, Guidant was required to notify J&J of the terms of that offer and give J&J five business days to make a competing offer, which Guidant would be required to consider before it could terminate the Merger Agreement without a breach.

(d) Boston Scientific Makes a Last-Minute Bid, and Guidant Breaches the Merger Agreement to Facilitate Turning It into a Superior Proposal

38. On December 5, 2005, before the merger between J&J and Guidant had closed, Boston Scientific announced a bid for Guidant, offering $25 billion, or $72 per share. While nominally higher in price than the J&J deal, Boston Scientific's offer was contingent upon, among other things, receiving regulatory approval and was therefore subject to uncertainty and delay.

39. On January 8, 2006, Boston Scientific submitted a formal proposal to acquire Guidant for $72 per share. As part of this formal offer, Boston Scientific also announced that it had entered into an agreement with Abbott to divest Guidant's VI and endovascular businesses to Abbott, as well as to share rights to Guidant's DES program, in order to facilitate prompt antitrust review and approval. Abbott also agreed to provide a $700 million loan to Boston Scientific.

40. Based on statements made in a January 9, 2006 conference call with analysts to discuss the Boston Scientific proposal, it became clear that Guidant had cooperated with and facilitated Boston Scientific's Takeover Proposal by impermissibly providing confidential information to Abbott. This in turn enabled Boston Scientific to enter into the agreement with Abbott, which was critical to Boston Scientific's ability to have its offer declared by Guidant as a Superior Proposal and thereby have it accepted in lieu of the J&J transaction.

41. On the conference call, Larry Best, Chief Financial Officer for Boston Scientific, emphasized the importance of the agreement with Abbott to Boston Scientific's Takeover Proposal. In Mr. Best's words, the Abbott agreement was "critically important not only for the quick completion of the Guidant acquisition but also for the business prospects of the combined company." Mr. Best explained: "As we said when we announced our initial proposal our intention was to divest Guidant's vascular intervention and endovascular business in an effort to obtain rapid antitrust approval for the Guidant acquisition. Therefore, we have executed a binding agreement with Abbott. Abbott will buy Guidant's VI and endovascular businesses when we complete this transaction with Guidant."

42. During the Q&A session at the end of the call, one analyst asked Boston Scientific's Chief Operating Officer, Paul LaViolette, whether Boston Scientific had "seen part of the [Guidant DES] data as a part of your due diligence and if not, is there some contingency that exists for Abbott should the [Guidant DES] data prove disappointing . . . ?"

43. Electing to respond to this question himself, Mr. Best was quoted as saying:

> Let me explain the due diligence process. As you can imagine, Guidant, you know was very protective of their program in terms of our doing due diligence. *We had the opportunity to do a certain level of due diligence. Abbott had the opportunity to do a much deeper dive on due diligence.* My understanding from their due diligence is that they were very impressed with the data and what they found, and that is how they came up with the valuation and the decision to move forward. (Emphasis added).

44. Thus, at some point in time between Boston Scientific's announcement of its bid for Guidant on December 5, 2005, and Boston Scientific's submission of a formal proposal on January 8, 2006, Guidant not only allowed Boston Scientific to conduct due diligence on it businesses but also disclosed even more confidential business information to Abbott — which had no independent right to receive any information and was prohibited from receiving any information under the Merger Agreement — about its VI and endovascular businesses.

45. As a result of the "deeper dive" it was permitted into Guidant's confidential business information, Abbott was able to make a "decision to move forward" and agree to acquire the entire VI business and other assets that Boston Scientific needed to divest to expedite antitrust regulatory approval of its proposed acquisition of Guidant. Without these

agreements, Boston Scientific's Takeover Proposal would not have been viable, much less superior to J&J's.

(e) Guidant's Impermissible Disclosures Constituted a Willful and Material Breach of the Merger Agreement

46. Immediately upon learning that Guidant had divulged confidential business information to Abbott, in breach of the No Solicitation provision of the Merger Agreement, J&J's General Counsel raised the issue with Guidant's General Counsel. In a follow-up letter dated January 23, 2006, J&J's General Counsel wrote to Guidant noting the apparent breach of Section 4.02 of their Merger Agreement and demanding an explanation. In response, Guidant's General Counsel attempted to justify Guidant's actions by, among other things, claiming that "Boston Scientific brought Abbott into the transaction as part of Boston Scientific's 'Takeover Proposal'" and that Abbott was a "joint bidder" for Guidant along with Boston Scientific. The matter remained unresolved.

47. Abbott was not a "joint-bidder" for Guidant. Abbott did not make a Takeover Proposal either on its own or in conjunction with Boston Scientific and, therefore, was not entitled to receive any confidential information from Guidant. Nor was Abbott a "Representative" of Boston Scientific, as that term is defined in Section 4.02 of the Merger Agreement. Rather, at all times Abbott was a third party divestiture candidate dealing at arms' length with Boston Scientific in negotiating the acquisition of certain businesses that would be divested in the event that Boston Scientific's Takeover Proposal was accepted.

48. As Boston Scientific itself noted during the January 9 conference call, an executed agreement with Abbott was critically important both to rapid antitrust approval of a potential acquisition by Boston Scientific and to the perceived business prospects of the

combined company. Just as J&J entered into a Licensing Agreement with Abbott in anticipation of closing its Merger Agreement with Guidant, Boston Scientific needed to enter into a much more extensive agreement with Abbott — divesting entire businesses — to ease antitrust approval of its own otherwise inferior proposal to acquire Guidant. By leaking confidential information to Abbott, a third-party divestiture candidate, Guidant, in violation of the No Solicitation restrictions in its Merger Agreement with J&J, thus knowingly and willfully facilitated Boston Scientific's Takeover Proposal becoming a Superior Proposal.

(f) Guidant Deems Boston Scientific's Offer to be a "Superior Proposal"

49. On January 10, 2006, Guidant's Board of Directors met to consider whether Boston Scientific's offer was a "Superior Proposal."

50. Faced with the prospect of losing the transaction that it had pursued for more than a year, J&J chose to reconsider the amount it was willing to offer for Guidant. On January 11, J&J and Guidant announced a revised Merger Agreement, raising the price to $68.06 per Guidant share. On the next day, however, Boston Scientific improved its own offer to $73 per Guidant share. The following day, January 13, 2006, J&J and Guidant announced a further revision to their Merger Agreement, raising the acquisition price to $71 per share, but once again, on January 17, 2006, Boston Scientific raised its offer, this time to $80 per share.

51. Later in the day on January 17, 2006, Guidant's Board announced that Boston's bid was deemed a "Superior Proposal" to the existing deal with J&J. On January 25, 2006, Guidant announced that it was terminating the Merger Agreement with J&J, as it was entitled to do upon determining that there was a Superior Proposal, and entering into an acquisition agreement with Boston Scientific for $27 billion. J&J ultimately received a $705

million "termination fee" under the terms of its Merger Agreement. However, as the Merger Agreement itself makes clear, "no such termination shall relieve any party hereto from any liability or damages resulting from the willful and material breach by a party of any of its representations, warranties, covenants or agreements set forth in this Agreement." (Merger Agreement at § 7.02).

52. As a result of Guidant's willful and material breach of the No Solicitation provision of the Merger Agreement, which facilitated Boston Scientific's Takeover Proposal through the prohibited confidential disclosures to third-party divestiture candidate Abbott, J&J was wrongfully deprived of the full benefits of its bargain and suffered damages that it now seeks to recover.

V. Claims for Relief

First Cause of Action for Breach of Contract (Against Defendant Guidant)

53. J&J repeats and realleges the allegations of paragraphs 1 to 52.

54. J&J entered into a valid, binding contract embodied in the Merger Agreement. A material term of the Merger Agreement was a "No Solicitation" clause, as set forth in Section 4.02 of the Merger Agreement. The No Solicitation clause was designed to protect the terms of the bargain that the parties struck, pending the closing of their transaction, while providing Guidant with the limited ability to receive and negotiate unsolicited alternative proposals.

55. Assuming that Boston Scientific's December 5, 2005 bid could be viewed as reasonably likely to lead to a Superior Proposal, Guidant was only permitted to provide confidential information to Boston Scientific and its Representatives, as defined in the Merger Agreement. Since Abbott was neither a person making a Takeover Proposal nor a Representative of Boston Scientific, but only a third-party divestiture candidate, permitting Abbott to take a "deeper dive" into Guidant's confidential information was a clear breach of the Merger Agreement.

56. This breach went to the heart of J&J's bargain, facilitating a competing bid by providing confidential information to a person not entitled to receive such information under the No Solicitation clause.

57. The breach was also material and harmed J&J. Had Abbott not been provided with Guidant's confidential business information, Abbott would not have been able to enter into the divestiture agreement, which in turn facilitated and enabled Boston Scientific's Takeover Proposal to be viewed as a Superior Proposal.

58. As a result of Guidant's willful and material breach, J&J was deprived of the benefit of its bargain under the Merger Agreement and suffered damages.

59. J&J made reasonable and diligent attempts to mitigate its damages.

Second Cause of Action
for Breach of the Implied Duty of Good Faith and Fair Dealing
(Against Defendant Guidant)

60. J&J repeats and realleges the allegations of paragraphs 1 to 52.

61. As a matter of common law, as well as the law of the State of Indiana, every contract imposes on the parties thereto an implied duty of good faith and fair dealing.

62. Defendant Guidant breached the implied duty of good faith and fair dealing by negotiating and facilitating a competing Takeover Proposal from another party, Boston Scientific, during the time that it was party to a binding Merger Agreement with J&J, in violation of the Merger Agreement.

63. Guidant could have terminated the Merger Agreement with J&J, paid the termination fee, and assumed the risk of being able to negotiate and enter into an alternative deal with Boston Scientific, subject to the uncertainty of being able to consummate a divestiture and the inevitable delay and uncertainty of antitrust regulatory review. Instead, Guidant surreptitiously facilitated an alternative proposal with Boston Scientific, through the prohibited disclosure of confidential information to Abbott, a third party divestiture candidate. Guidant thus used the Merger Agreement to negotiate a better offer in breach of its implied duty of good faith and fair dealing.

64. As a result of Guidant's breach of the implied duty of good faith and fair dealing, J&J was deprived of the benefit of its bargain under the Merger Agreement and suffered damages.

Third Cause of Action
For Tortious Interference with Contract
(Against Defendants Boston Scientific and Abbott)

65. J&J repeats and realleges herein the allegations of paragraphs 1 to 52.

66. Boston Scientific and Abbott were aware that J&J had entered into a binding Merger Agreement with Guidant and were aware that the Merger Agreement prohibited the disclosure of confidential information to third parties.

67. Boston Scientific and Abbott intentionally induced Guidant to breach the Merger Agreement with J&J by disclosing confidential business information to Abbott.

68. Boston Scientific and Abbott thus knowingly, intentionally, and maliciously interfered with J&J's binding contract to acquire Guidant under the terms of the Merger Agreement that was on the verge of closing.

69. Abbott emerged from its prohibited due diligence review with a clear picture of Guidant's businesses that enabled it to proceed expeditiously with a divestiture agreement, which in turn facilitated Boston Scientific's ability to make a "Superior Proposal" to Guidant.

70. As a result of Guidant's breaches and Boston Scientific's and Abbott's tortious interference with J&J's Merger Agreement and prospective business opportunity, J&J was damaged.

Prayer for Relief

Wherefore, Plaintiff J&J respectfully requests the following relief:

(i) that the Court find that Guidant willfully and materially breached the Merger Agreement with J&J;

(ii) that the Court find that Guidant breached the implied obligation of good faith and fair dealing; and

(iii) that the Court find that Boston Scientific and Abbott knowingly, intentionally and tortiously interfered with, and induced Guidant to breach, the Merger Agreement;

(iv) that after making such determinations, the Court award Plaintiff appropriate legal damages (general and special), in an amount to be determined at trial, but in no event less than $5.5 billion; and

(v) that the Court award such other necessary and proper relief, including, without limitation, attorneys' fees, interest, costs, as the Court may deem just and proper.

Dated: New York, New York
September 25, 2006

Kramer Levin Naftalis & Frankel LLP

By: _____
Harold P Weinberger (HW3240)
Timothy J. Helwick (TH5833)

1177 Avenue of the Americas
New York, New York 10036
Telephone: (212) 715-9000

Attorneys for Plaintiff Johnson & Johnson

Exhibit A

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ABBOTT LABORATORIES and ABBOTT CARDIOVASCULAR SYSTEMS, INC.,	)	
Plaintiffs,	)	
v.	)	C. A. No. 06-613-SLR
JOHNSON AND JOHNSON, INC. and CORDIS CORPORATION,	)	
Defendants.	)	

[PROPOSED] ORDER GRANTING PLAINTIFFS' MOTION, SUPPLEMENTAL MOTION AND SECOND SUPPLEMENTAL MOTION FOR LEAVE TO FILE A SUPPLEMENTAL COMPLAINT

At Wilmington this _____ day of _____, 2007, having considered Plaintiffs' Motion (D.I. 43), Supplemental Motion (D.I. 51), and Second Supplemental Motion For Leave To File A Supplemental Complaint Or In The Alternative To Consolidate Related Actions (the "First," "Second," and "Third" Motion to Supplement, respectively),

IT IS HEREBY ORDERED that Plaintiffs' Motions to Supplement are GRANTED. Within 10 days of entry of this Order, Plaintiffs may file a Supplemental and Amended Complaint substantially in the form as Exhibit 1 filed in support of Plaintiffs' Third Motion to Supplement. With the exception of Claims V and VI, the Supplemental and Amended Complaint shall be deemed filed as of the filing of the First Motion to Supplement. Claim V shall be deemed filed as of the filing of the Second

Motion to Supplement. Claim VI shall be deemed filed as of the filing of the Third Motion to Supplement.

_____
Chief Judge

Exhibit B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ABBOTT LABORATORIES and ABBOTT CARDIOVASCULAR SYSTEMS, INC.,	)	
Plaintiffs,	)	
v.	)	C. A. No. 06-613-SLR
JOHNSON AND JOHNSON, INC. and CORDIS CORPORATION,	)	
Defendants.	)	

[PROPOSED] ORDER GRANTING PLAINTIFFS' MOTION, SUPPLEMENTAL MOTION, AND SECOND SUPPLEMENTAL MOTION TO CONSOLIDATE RELATED ACTIONS AND GRANTING PLAINTIFFS' MOTION FOR LEAVE TO FILE A SUPPLEMENTAL COMPLAINT

At Wilmington this _____ day of _____, 2007, having considered (1) Plaintiffs' Motion For Leave To File A Supplemental Complaint Or In The Alternative To Consolidate Related Actions filed in Civil Action No. 06-613-SLR (D.I. 43, "Plaintiffs' 06-613 Motion to Consolidate"), renewed in two supplemental motions (D.I. 51 and D.I. filed on June 12, 2007); (2) Plaintiffs' Motion For Leave To File A Supplemental Complaint filed in Civil Action No. 07-259-SLR (D.I. 10, "Plaintiffs' 07-259 First Motion to Supplement"); and (3) Plaintiffs' Supplemental Motion For Leave To File A Supplemental Complaint filed in Civil Action No. 07-259-SLR on June 12, 2007 ("Plaintiffs' 07-259 Second Motion to Supplement"),

IT IS HEREBY ORDERED that Plaintiffs' 07-259 First and Second Motions to Supplement are GRANTED. Within 10 days of entry of this Order, Plaintiffs may file a Supplemental and Amended Complaint substantially in the form as Exhibit 1 filed in

support of Plaintiffs' 07-259 Second Motion to Supplement. With the exception of Claim III, Plaintiffs' Supplemental and Amended Complaint shall be deemed filed as of the filing of Plaintiffs' 07-259 First Motion to Supplement. Claim III shall be deemed filed as of the filing of Plaintiffs' 07-259 Second Motion to Supplement.

IT IS HEREBY ORDERED that Plaintiffs' 06-613 Motion to Consolidate is GRANTED. Civil Action No. 07-259-SLR, filed on May 15, 2007, is hereby consolidated with Civil Action No. 06-613-SLR. Civil Action No. 07-259-SLR shall be deemed filed as of the filing of Plaintiffs' 06-613 Motion to Consolidate.

_____
Chief Judge

IN THE UNITED STATES DISTRICT COURT FOR THE
DISTRICT OF DELAWARE

ABBOTT LABORATORIES and ~~ADVANCED~~ABBOTT CARDIOVASCULAR SYSTEMS, INC.,	)	Civil Action No. 06-613-SLR
Plaintiffs,	)	
v.	)	**JURY TRIAL DEMANDED**
JOHNSON AND JOHNSON, INC. and CORDIS CORPORATION,	)	
Defendants.	)	

SUPPLEMENTAL AND AMENDED COMPLAINT FOR DECLARATORY JUDGMENT OF PATENT INVALIDITY AND NONINFRINGEMENT

Plaintiffs Abbott Laboratories and ~~Advanced~~Abbott Cardiovascular Systems, Inc. (collectively "Abbott") bring this Supplemental and Amended Complaint against Defendants Johnson and Johnson, Inc. and Cordis Corporation (collectively "J&J"). This is an action for a declaratory judgment and injunctive relief that United States Patent No. 6,585,764 entitled "Stent With Therapeutically Active Dosage Of Rapamycin Coated Thereon" (the "Wright '764 patent"), United States Patent No. 6,808,536 entitled "Stent Containing Rapamycin Or Its Analogs Using A Modified Stent" (the "Wright '536 patent"), ~~and~~ United States Patent No. 6,776,796 entitled "Antiinflammatory Drug and Delivery Device" (the "Falotico '796 patent"), United States Patent No. 7,217,286 entitled "Local Delivery of Rapamycin for Treatment of Proliferative Sequelae Associated with PTCA Procedures, Including Delivery Using a Modified Stent" (the "Wright '7286 patent "), United States Patent No. 7,223,286 entitled "Local Delivery Of Rapamycin For Treatment Of Proliferative Sequelae Associated With PTCA Procedures, Including Delivery Using A Modified Stent" (the "Wright '3286 patent"), and United States

Patent No. 7,229,473 entitled "Local Delivery of Rapamycin for Treatment of Proliferative Sequelae Associated with PTCA Procedures, Including Delivery Using a Modified Stent" (the "Wright '473 patent") are invalid and not infringed by Abbott. The Wright '764 patent, the Wright '536 patent, ~~and~~ the Falotico '796 patent, the Wright '7286 patent, and the Wright '3286 patent are attached as Exhibits A – ~~C~~E, respectively. The Issue Notification for the Wright '473 patent and the Wright '473 patent are attached as Exhibit F. Abbott alleges as follows:

THE PARTIES

1. Abbott Laboratories is a corporation organized under the laws of the State of Illinois and has a principal place of business at 100 Abbott Park Road, North Chicago, Illinois.

2. ~~Advanced~~Abbott Cardiovascular Systems, Inc. ("ACS"), formerly Advanced Cardiovascular Systems, Inc., is a corporation organized under the laws of the State of California and has a principal place of business at 3200 Lakeside Drive, Santa Clara, California. ACS is a subsidiary of Abbott Laboratories.

3. On information and belief, Johnson and Johnson, Inc. is a corporation organized under the laws of the State of New Jersey and has a principal place of business at One Johnson and Johnson Plaza, New Brunswick, New Jersey.

4. On information and belief, Cordis Corporation ("Cordis") is a corporation organized under the laws of the State of Florida and has a principal place of business in Miami Lakes, Florida. Cordis is a subsidiary of Johnson and Johnson, Inc.

JURISDICTION AND VENUE

5. This action arises under the Patent Laws of the United States (35 U.S.C. § 1 *et seq.*).

6. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

7. This Court has personal jurisdiction, general and specific, over J&J.

8. On information and belief, J&J has systematic and continuous contacts in this judicial district.

9. On information and belief, J&J regularly avails itself of the benefits of this judicial district, including the jurisdiction of the courts.

10. On information and belief, J&J regularly transacts business within this judicial district.

11. On information and belief, J&J regularly sells products in this judicial district. J&J derives substantial revenues from sales in this district.

12. Venue is proper in this district under 28 U.S.C. §§ 1391(b) and (c).

BACKGROUND

13. J&J, and in particular Cordis, directly competes with Abbott in the field of intravascular stents used to treat coronary artery disease.

14. The coronary stent industry is highly litigious. J&J, and in particular Cordis, has a well-known history of suing competitors in this field for patent infringement.

15. On three occasions within the last ten years, Cordis sued ACS in this district, alleging patent infringement involving angioplasty catheters or stents for treating coronary artery disease. (*Cordis Corporation, et al. v. Advanced Cardiovascular Systems, Inc, et al.*, C.A. No.

97-550-SLR; *Cordis Corporation, et al. v. Advanced Cardiovascular Systems, Inc., et al.*, C.A. No. 97-635-SLR; and *Cordis Corporation, et al. v. Advanced Cardiovascular Systems, Inc., et al.*, C.A. No. 98-065-SLR).

16. On three additional occasions within the last ten years, Cordis initiated patent infringement actions in this judicial district involving angioplasty catheters or stents for treating coronary artery disease. (*Cordis Corp. v. Boston Scientific Corp.*, C.A. No. 98-197-SLR; *Cordis Corp. v. Medtronic AVE, Inc.*, C.A. No. 00-886-SLR; and *Cordis Corp. v. Boston Scientific Corp.*, C.A. No. 03-027-SLR).

17. ~~16.~~ In early 2006, J&J and Boston Scientific Corporation ("BSC") each were bidding to acquire assets of Guidant Corporation ("Guidant"), which at the time was the parent corporation of ACS. In conjunction with BSC's bid, ACS would be acquired by Abbott Laboratories, which was the ultimate result.

18. ~~17.~~ One of the key assets of ACS was the XIENCE V drug eluting stent system ("XIENCE V"), which elutes a proprietary drug known as everolimus. ACS holds an exclusive patent license to use everolimus for drug eluting stents. In clinical trials, everolimus has proven superior to other drugs.

19. ~~18.~~ On information and belief, J&J believed in early 2006 that the XIENCE V would be launched within a few months.

J&J's Public Threats To Sue For Patent Infringement By XIENCE V

20. ~~19.~~ On information and belief, J&J undertook a public campaign to cast a cloud over the launch of the XIENCE V.

21. ~~20.~~ On information and belief, as a main thrust of this public campaign, J&J alleged that the XIENCE V would infringe patents allegedly owned by J&J and that J&J would

sue Abbott for infringement by the XIENCE V following its launch. On information and belief, J&J's allegations related to at least the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

22. ~~21.~~ On information and belief, J&J broadcasted threatening statements to industry analysts regarding alleged infringement by XIENCE V, for publication in furtherance of J&J's public campaign.

23. ~~22.~~ For example, the Prudential Equity Group, LLC published a report on January 20, 2006, titled "JNJ: Takes Off The Gloves In Its Fight With Boston Scientific For Guidant," attached as Exhibit ~~D~~G ("the Prudential report"). In the Prudential report, parties are identified by their stock symbols: ABT for Abbott, GDT for Guidant, JNJ for J&J, and BSX for BSC.

24. ~~23.~~ On information and belief, the Prudential report relied on information provided in pertinent part by J&J.

25. ~~24.~~ Among other things, the Prudential report stated:

> JNJ claims that 2 of its patents may be infringed if a company tries to launch a drug-eluting stent coated with a rapamycin derivative such as . . . GDT's everolimus. The potential for JNJ to prevent ABT and BSX from marketing the Xience-V DES, could give the GDT board pause for approving a BSX-GDT merger.
>
> * * *
>
> If BSX acquires GDT, BSX would sell GDT's vascular intervention (VI) business, including shared rights to GDT's promising everolimus-coated stent, Xience-V, to ABT. Although JNJ's patents have never been litigated, JNJ believes it has a strong intellectual property (IP) position with regard to the use of

> rapamycin derivatives on a stent. JNJ could pursue a preliminary injunction if ABT and BSX try to launch an everolimus-coated . . . stent. . . . According to JNJ, the key patents are the Falotico (6,776,796) and Wright (6,585,764) patents.

26. ~~25.~~ On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Prudential analysts.

27. ~~26.~~ On January 23, 2006, A.G. Edwards & Sons, Inc. published a report titled "Healthcare Industry Note: The Game May Be Far From Over," attached as Exhibit ~~E~~H ("the AG Edwards report").

28. ~~27.~~ On information and belief, the AG Edwards report relied on information provided in pertinent part by J&J.

29. ~~28.~~ Among other things, the AG Edwards report stated:

> We have had conversations with Johnson & Johnson (JNJ) and Boston Scientific (BSX) and others recently that lead us to believe that the Guidant (GDT) game is far from over.
>
> * * *
>
> We were also reminded by JNJ that it had three patents related to '-limus' compounds that it thought precluded any other company from using such a compound on a stent. We were only given two patent numbers (6776796 [the Falotico '796 patent] and 6585764 [the Wright '764 patent]) . . . .

30. ~~29.~~ On information and belief, the third patent referenced in J&J's threatening statements was the Wright '536 patent.

31. ~~30.~~ On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to AG Edwards analysts.

32. On January 13, 2006, Citigroup published a report titled "An INTERESTing New Offer," attached as Exhibit I ("the January 13, 2006 Citigroup report").

33. On information and belief, the January 13, 2006 Citigroup report relied on information provided in pertinent part by J&J.

34. Among other things, the January 13, 2006 Citigroup report stated:

> The [Wright and Falotico] patents have never been challenged or enforced because no other company has launched a limus-based drug-eluting stent in the US, but are likely to eventually lead to litigation.

35. Citigroup published an additional report on March 23, 2006 titled "Deconstructing Xience," attached as Exhibit J ("the March 23, 2006 Citigroup report"). In the March 23, 2006 Citigroup report J&J is identified by its stock symbol JNJ.

36. On information and belief, the March 23, 2006 Citigroup report relied on information provided in pertinent part by J&J.

37. Among other things, the March 23, 2006 Citigroup report stated:

> Everolimus will likely face two IP challenges from JNJ as both its Falotico and Wright patents claim the use of a limus analogue on a stent.

38. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Citigroup analysts.

39. On January 30, 2006, Lehman Brothers published a report titled "BSX: The Risks – Part I," attached as Exhibit K ("the Lehman Brothers report"). In the Lehman Brothers report, parties are identified by their stock symbols: ABT for Abbott; GDT for Guidant; and JNJ for J&J.

40. On information and belief, the Lehman Brothers report relied on information provided in pertinent part by J&J.

41. Among other things, the Lehman Brothers report stated:

> There are even hypothetical litigations to contend with as JNJ has strongly suggested that they feel GDT and ABT may violate JNJ/Wyeth DES patents covering the "limus" family of drugs.

42. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Lehman Brothers analysts.

43. On March 14, 2006, Merrill Lynch published a report titled "More legal wrangling for J&J possible," attached as Exhibit L ("the Merrill Lynch report"). In the Merrill Lynch report, J&J is identified by its stock symbol JNJ.

44. On information and belief, the Merrill Lynch report relied on information provided in pertinent part by J&J.

45. Among other things, the Merrill Lynch report stated:

> JNJ has two patents (Wright and Falotico) which appear to relate to the elution of characteristics of "olimus" compounds; JNJ's Cypher DES uses sirolimus, a member of the olimus family of drugs; other olimus drugs include Guidant's everolimus and Abbott/Medtronic's zotarolimus (ABT-578). The European launch of Guidant's Xience DES, which the company has targeted for Q2:06, could trigger possible legal activity since we understand U.S. patent law prohibits domestic manufacture of a product for sale outside the U.S. if there's been infringement of intellectual property.

46. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Merrill Lynch analysts.

47. On information and belief, J&J broadcast threatening statements to other news outlets regarding alleged infringement by XIENCE V, for publication in furtherance of J&J's public campaign.

48. ~~31.~~ On January 23, 2006, the International Herald Tribune published an article headlined "J&J works to discredit rival offer for Guidant," attached as Exhibit ~~F~~M ("the International Herald article").

49. ~~32.~~ On information and belief, the International Herald article relied on information provided in pertinent part by J&J.

50. ~~33.~~ Among other things, the International Herald article stated:

> "J&J is communicating to the Street that Boston Scientific's $80-a-share offer for Guidant is fraught with uncertainty," Lawrence Biegelsen, an analyst with Prudential in New York, said in a note to clients sent on Friday.
>
> * * *
>
> Johnson & Johnson's campaign consists of telling analysts and shareholders that Boston Scientific is in over its head and is tempting patent litigation that may undercut Boston Scientific's plans.
>
> "They're trying to tell all of us that there are patents out there that they have that they feel can stop Boston Scientific," said Jan David Wald, an analyst with A.G. Edwards. Wald said he had been called by a Johnson & Johnson employee, whom he declined to name.

> Johnson & Johnson told analysts it was considering filing patent infringement lawsuits over stent drug coatings to keep Boston Scientific and its bidding partner, Abbott Laboratories, from profiting from the new Guidant devices, according to Biegelsen of Prudential.
>
> * * *
>
> Boston Scientific and J&J have been fighting in court for years over patent-infringement cases related to stent design. At the moment, the two companies are alone in the U.S. stent market, with Boston Scientific holding a 55 percent share.
>
> * * *
>
> The potential for Johnson & Johnson to prevent Abbott and Boston Scientific from marketing Guidant's next-generation heart stent "could give the Guidant board pause for approving a Boston Scientific-Guidant merger," Biegelsen said. "J&J claims that two of its patents may be infringed if a company tries to launch a drug-eluting stent coated with" . . . Guidant's everolimus, he wrote.

51. On January 20, 2006, the Boston Globe published an article headlined "Suitors take Guidant fight to The Street," attached as Exhibit N ("the Boston Globe article").

52. On information and belief, the Boston Globe article relied on information provided in pertinent part by J&J.

53. Among other things, the Boston Globe article stated:

> [J&J] has also raised the prospect that it could use patents and existing ties to Guidant to derail or complicate Boston Scientific's offer, said Matthew Dodds, an analyst for Citigroup who is skeptical about Guidant's value to both companies.

54. Also on January 20, 2006, Crain's Chicago Business published an article headlined "Abbott stock falls on concerns over success of Guidant bid," attached as Exhibit O ("the Crain's article").

55. On information and belief, the Crain's article relied on information provided in pertinent part by J&J.

56. Among other things, the Crain's article stated:

> The analyst, Prudential Equity Group, LLC's Larry Biegelsen, reported that Guidant's board could balk at Boston Scientific and Abbott's joint bid because Johnson & Johnson, a competing bidder for Guidant, claims its patents would be violated if Abbott markets its own drug-eluting stents or those made by Guidant.

57. On January 21, 2006, Reuters published an article headlined "Abbott, Boston shares off on J&J patent threat," attached as Exhibit P ("the Reuters article").

58. On information and belief, the Reuters article relied on information provided in pertinent part by J&J.

59. Among other things, the Reuters article stated:

> One analyst, who asked not to be named, said J&J management was making rounds on Wall Street trying to fan fears about the Boston Scientific bid.
>
> The analyst said J&J was arguing that Boston Scientific's bid was breaking its bank, that its assumptions on Guidant's cardiac rhythm management were too aggressive and that there was intellectual property infringement that would limit potential of important products.

60. On January 24, 2006, Medical Device Daily published an article headlined "J&J offer rumors persist as Guidant has more ICD issues," attached as Exhibit Q ("the Medical Device Daily article").

61. On information and belief, the Medical Device Daily article relied on information provided in pertinent part by J&J.

62. Among other things, the Medical Device Daily article stated:

> Fueling this speculation were rumors, some of which apparently were planted by J&J personnel as part of an organized campaign to undermine the Boston Scientific offer in the minds of analysts, that two of its patents may be infringed if an unnamed company tries to launch a drug-eluting stent coated with a derivative of rapamycin.

63. On January 26, 2006, The Wall Street Journal published an article headlined "Boston Scientific Faces Pivotal Test After Victory in Fight for Guidant," attached as Exhibit R ("the Wall Street Journal article").

64. On information and belief, the Wall Street Journal article relied on information provided in pertinent part by J&J.

65. Among other things, the Wall Street Journal article stated that:

> Another potential wrinkle arises in the intellectual-property rights surrounding stents -- an area that's been the subject of extensive litigation in the industry. Citigroup analyst Matthew Dodds says J&J holds patents on methods of using "limus"-type drugs on stents -- including the everolimus on Guidant's stent, as well as a drug on an Abbott stent.

66. ~~34.~~ On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to analysts and others.

67. ~~35.~~ On information and belief, J&J made additional threatening statements to industry analysts, asserting that J&J could prevent Abbott from making or selling the XIENCE V by suing for infringement of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent. On information and belief, J&J anticipated and intended that Abbott and others would become aware of these threatening statements.

68. Abbott and others did become aware of J&J's threatening statements.

69. For example, on January 20, 2006, Avram Goldstein of Bloomberg contacted Abbott regarding the Wright and Falotico patents in relation to XIENCE V.

70. On January 13, 2006, Bruce Nudell of Sanford C. Bernstein contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

71. Also on January 13, 2006, The Shaw Group contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

72. On January 20, 2006, Avram Goldstein of Bloomberg contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

73. Again on January 20, 2006, Barnaby Feder of the New York Times contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

74. On January 31, 2006, Steve Silva of Joele Frank contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

75. On March 23, 2006, Jennifer B. Pearlman of Burgundy Asset Management contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

76. On information and belief, in furtherance of its campaign to cast a cloud over the launch of XIENCE V, J&J made threatening statements to Guidant.

77. On January 12, 2006, J&J contacted Guidant and informed Guidant that if Boston Scientific acquired Guidant, Abbott and Boston Scientific would have problems with the Wright and Falotico patent families.

78. On January 13, 2006, J&J again contacted Guidant. J&J sent Guidant a document asserting that J&J's intellectual property portfolio included patents directed to everolimus when used on a stent, Abbott would not receive access to these patents in the event that Boston Scientific were to acquire Guidant, and any drug eluting stent using everolimus, including XIENCE V, may infringe these patents.

79. On information and belief, J&J intended to create a substantial controversy between J&J and Abbott regarding XIENCE V's alleged infringement of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

80. ~~36.~~ On information and belief, J&J intended to create the apprehension in Abbott and others that J&J would sue Abbott, following the launch of the XIENCE V, asserting that the XIENCE V allegedly infringes the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

81. ~~37.~~ In March 2006, Guidant publicly announced that the XIENCE V launch would be delayed due to an issue related to manufacturing.

82. ~~38.~~ As of the date of ~~this~~the original Complaint, the XIENCE V launch ~~is~~was imminent. On information and belief, J&J ~~is~~was aware that the XIENCE V launch ~~is~~was imminent and ~~is~~was preparing to sue Abbott for infringement by the XIENCE V of the Wright

'764 patent, the Wright '536 patent, and the Falotico '796 patent. The XIENCE V subsequently launched in Europe.

83. ~~39.~~ On information and belief, J&J has never withdrawn or retracted any of its threatening statements that, following the launch of the XIENCE V, J&J would sue Abbott for infringement of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

84. On information and belief, by these statements J&J intended to create a substantial controversy between J&J and Abbott regarding alleged infringement of patents in the Wright and/or Falotico families by XIENCE V.

85. On information and belief, by these statements J&J intended to create the apprehension in Abbott and others that J&J would sue Abbott, following the launch of XIENCE V, asserting that XIENCE V allegedly infringes patents in the Wright and/or Falotico families.

J&J's Assertions In The Patent Office Of Infringement By XIENCE V

86. ~~40.~~ On August 7, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the First Wright Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 10/951,385 ("Wright '385 application"). The Wright '385 application is related to the Wright '764 patent ~~and~~, the Wright '536 patent, the Wright '7286 patent, and the Wright '473 patent. On May 29, 2007, the Wright '385 application issued as the Wright '3286 patent. A copy of the First Wright Petition is attached as Exhibit ~~G~~S.

87. ~~41.~~ In the First Wright Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Wright '385 application as a patent. Among other things, counsel for J&J asserted:

> Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch ~~the~~ XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).
>
> * * *
>
> I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of at least claims 103 and 130 on file in this application.
>
> * * *
>
> It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of at least claims 103 and 130 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

88. ~~42.~~ The subject matter of at least claim 103 of the Wright '385 application overlaps with subject matter claimed in the Wright '764 patent and the Wright '536 patent. Claim 103 of the Wright '385 application issued on May 29, 2007 as claim 40 of the Wright '3286 patent.

89. On information and belief, the subject matter claimed in the Wright '3286 patent is not patentably distinct from subject matter claimed in at least the Wright '7286 patent, the Wright '764 patent, the Wright '536 patent, and/or the Wright '473 patent.

90. On August 24, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the Second Wright Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 11/466,983 ("the Wright '983

application"). The Wright '983 application is related to the Wright '764 patent, the Wright '536 patent, and the Wright '3286 patent. On information and belief, on June 12, 2007, the Wright '983 application issued as the Wright '473 patent. A copy of the Second Wright Petition is attached as Exhibit T.

91. In the Second Wright Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Wright '983 application as a patent. In the Second Wright Petition, J&J's counsel made assertions substantially identical to the assertions made in connection with the First Wright Petition. (*See supra* ¶ 87).

92. The subject matter of at least claim 1 of the Wright '983 application overlaps with subject matter claimed in the Wright '764 patent.

93. On information and belief, the subject matter claimed in the Wright '473 patent is not patentably distinct from subject matter claimed in at least the Wright '7286 patent, the Wright '3286 patent, the Wright '764 patent, and/or the Wright '536 patent.

94. On August 24, 2006, J&J filed another "Petition to Make Special Because of Actual Infringement" ("the Third Wright Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 11/467,035 ("the Wright '035 application"). The Wright '035 application is related to the Wright '764 patent, the Wright '536 patent, and the Wright '3286 patent. On May 15, 2007, the Wright '035 application issued as the Wright '7286 patent. A copy of the Third Wright Petition is attached as Exhibit U.

95. In the Third Wright Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Wright '035 application as a patent. In the Third Wright Petition, J&J's counsel made assertions substantially identical to the assertions made in connection with the First Wright Petition. (*See supra* ¶ 87).

96. The subject matter of at least claim 1 of the Wright '7286 patent overlaps with subject matter claimed in the Wright '764 patent.

97. The subject matter claimed in the Wright '7286 patent is not patentably distinct from subject matter claimed in at least the Wright '3286 patent, the Wright '473 patent, the Wright '764 patent, and/or the Wright '536 patent.

98. ~~43.~~ On information and belief, J&J is preparing to assert, and has asserted, one or more patents in the Wright family, including at least the Wright '764 patent ~~and~~, the Wright '536 patent, the Wright '7286 patent, the Wright '3286 patent, and the Wright '473 patent against the XIENCE V ~~following its imminent launch~~.

99. ~~44.~~ On August 7, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the First Falotico Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 10/829,074 ("the Falotico '074 application"). The Falotico '074 application is related to the Falotico '796 patent. A copy of the First Falotico Petition is attached as Exhibit ~~H~~V.

100. ~~45.~~ In the First Falotico Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Falotico '074 application as a patent. Among other things, counsel for J&J asserted:

> Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch ~~the~~ XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).
>
> * * *
>
> I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases and other publicly available documents, with the claims of

the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of claims 15 to 30 on file in this application.

* * *

It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of claims 15 to 30 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

101. ~~46.~~ The subject matter of at least claim 15 of the Falotico '074 application overlaps with subject matter claimed in the Falotico '796 patent.

102. On August 7, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the Second Falotico Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 10/852,517 ("the Falotico '517 application"). The Falotico '517 application is related to the Falotico '796 patent. A copy of the Second Falotico Petition is attached as Exhibit W.

103. In the Second Falotico Petition, J&J asserted that it could sue Abbott for infringement by XIENCE V immediately upon issuance of the Falotico '517 application as a patent. In the Second Falotico Petition, J&J's counsel made assertions substantially identical to the assertions made in connection with the First Falotico Petition. (*See supra* ¶ 100).

104. The subject matter of at least claim 5 of the Falotico '517 application overlaps with subject matter claimed in the Falotico '796 patent.

105. On August 24, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the Third Falotico Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 11/467,099 ("the Falotico '099

application"). The Falotico '099 application is related to the Falotico '796 patent. A copy of the Third Falotico Petition is attached as Exhibit X.

106. In the Third Falotico Petition, J&J asserted that it could sue Abbott for infringement by XIENCE V immediately upon issuance of the Falotico '099 application as a patent. In the Third Falotico Petition, J&J's counsel made assertions substantially identical to the assertions made in connection with the First Falotico Petition. (*See supra* ¶ 100).

107. The subject matter of at least claim 1 of the Falotico '099 application overlaps with subject matter claimed in the Falotico '796 patent.

108. ~~47.~~ On information and belief, J&J is preparing to assert one or more patents in the Falotico family, including at least the Falotico '796 patent, against the XIENCE V ~~following its imminent launch~~.

J&J Has Recently Sued Abbott In An Attempt To Interfere With The XIENCE V Launch

109. ~~48.~~ On September 25, 2006, J&J filed a complaint in the District Court for the Southern District of New York. Among other things, J&J alleges that Abbott Laboratories tortiously interfered with J&J's intended acquisition of Guidant. The complaint seeks no less than $5.5 billion in damages. A copy of the complaint is attached as Exhibit ~~I~~Y.

110. ~~49.~~ Although the events cited in the complaint occurred over eight months ago, J&J timed the lawsuit, on information and belief, in anticipation of the then imminent launch of XIENCE V. Both the timing of the lawsuit and the amount of the damages claimed manifest J&J's intent to cast a cloud over Abbott and interfere with the then imminent launch of the XIENCE V.

The XIENCE V Launch ~~Is Imminent~~

111. ~~50.~~ As of the date of ~~this~~the original Complaint, Abbott ~~will have~~had manufactured, at its facilities in the United States, thousands of XIENCE V products to support its ~~imminent~~ launch.

112. ~~51.~~ Abbott ~~will continue~~has continued to manufacture XIENCE V at its facilities in the United States following the launch.

113. J&J created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Wright '764 patent, the Wright '536 patent, the Falotico '796 patent, the Wright '7286 patent, the Wright '3286 patent, and the Wright '473 patent by XIENCE V.

114. ~~52.~~ Abbott has a reasonable apprehension that J&J intends to sue Abbott for infringement of the Wright '764 patent, the Wright '536 patent, ~~and~~the Falotico '796 patent, the Wright '7286 patent, the Wright '3286 patent, and the Wright '473 patent by XIENCE V ~~following its imminent launch~~.

CLAIM I

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 6,585,764

115. ~~53.~~ Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-~~52.~~114.

116. J&J's actions have created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Wright '764 patent by XIENCE V.

117. J&J has asserted rights under the Wright '764 patent against the XIENCE V.

118. ~~54.~~ J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '764 patent by XIENCE V.

119. ~~55.~~ On information and belief, the claims of the Wright '764 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

120. ~~56.~~ The XIENCE V does not infringe any valid claim of the Wright '764 patent.

121. ~~57.~~ An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '764 patent.

CLAIM II

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 6,808,536

122. ~~58.~~ Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-~~57.~~121.

123. J&J's actions have created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Wright '536 patent by XIENCE V.

124. J&J has asserted rights under the Wright '536 patent against the XIENCE V.

125. ~~59.~~ J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '536 patent by XIENCE V.

126. ~~60.~~ On information and belief, the claims of the Wright '536 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

127. ~~61.~~ The XIENCE V does not infringe any valid claim of the Wright '536 patent.

128. ~~62.~~ An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '536 patent.

CLAIM III

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 6,776,796

129. ~~63.~~ Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-~~62.~~128.

130. J&J's actions have created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Falotico '796 patent by XIENCE V.

131. J&J has asserted rights under the Falotico '796 patent against the XIENCE V.

132. ~~64.~~ J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Falotico '796 patent by XIENCE V.

133. ~~65.~~ On information and belief, the claims of the Falotico '796 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

134. ~~66.~~ The XIENCE V does not infringe any valid claim of the Falotico '796 patent.

135. ~~67.~~ An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Falotico '796 patent.

CLAIM IV

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 7,217,286

136. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-135.

137. The Wright '7286 patent issued on May 15, 2007.

138. J&J's actions have created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Wright '7286 patent by XIENCE V.

139. J&J has asserted rights under the Wright '7286 patent against the XIENCE V.

140. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '7286 patent by XIENCE V.

141. On information and belief, the claims of the Wright '7286 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

142. The XIENCE V does not infringe any valid claim of the Wright '7286 patent.

143. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '7286 patent.

CLAIM V

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 7,223,286

144. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-143.

145. The Wright '3286 patent issued on May 29, 2007.

146. J&J's actions have created a substantial controversy between J&J and Abbott regarding alleged infringement of the Wright '3286 patent by XIENCE V.

147. J&J has asserted rights under the Wright '3286 patent against the XIENCE V.

148. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '3286 patent by XIENCE V.

149. On information and belief, the claims of the Wright '3286 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

150. The XIENCE V does not infringe any valid claim of the Wright '3286 patent.

151. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '3286 patent.

CLAIM VI

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 7,229,473

152. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-151.

153. On information and belief, the Wright '473 patent issued on June 12, 2007.

154. J&J's actions have created a substantial controversy between J&J and Abbott regarding alleged infringement of the Wright '473 patent by XIENCE V.

155. J&J has asserted rights under the Wright '473 patent against the XIENCE V.

156. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '473 patent by XIENCE V.

157. On information and belief, the claims of the Wright '473 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

158. The XIENCE V does not infringe any valid claim of the Wright '473 patent.

159. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '473 patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request entry of judgment in their favor that:

(a) each and every claim of U.S. Patent No. 6,585,764 is invalid;

(b) each and every claim of U.S. Patent No. 6,808,536 is invalid;

(c) each and every claim of U.S. Patent No. 6,776,796 is invalid;

(d) each and every claim of U.S. Patent No. 7,217,286 is invalid;

(e) each and every claim of U.S. Patent No. 7,223,286 is invalid;

(f) each and every claim of U.S. Patent No. 7,229,473 is invalid;

(g) ~~(d)~~ Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 6,585,764;

(h) ~~(e)~~ Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 6,808,536;

(i) ~~(f)~~ Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 6,776,796;

(j) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 7,217,286;

(k) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 7,223,286;

(l) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 7,229,473;

(m) ~~(g)~~ Defendants and their officers, agents, employees, representatives, counsel and all persons in active concert or participation with any of them, directly or indirectly, be enjoined from threatening or charging infringement of, or instituting any action for infringement of any of U.S. Patent Nos. 6,585,764, 6,808,536, ~~and 6,776,796~~6,776,796, 7,217,286, 7,223,286, and 7,229,473 against Plaintiffs, their suppliers, customers, distributors or users of their products;

(n) ~~(h)~~ Defendants pay to Plaintiffs the costs and reasonable attorneys fees incurred by Plaintiffs in this action; and

(o) ~~(i)~~ Plaintiffs be granted such other and further relief as this Court deems just and proper.

JURY TRIAL DEMANDED

Plaintiffs demand a trial by jury on all issues so triable.

OF COUNSEL:
Edward A. Mas II
Leland G. Hansen
Sandra A. Frantzen
Christopher J. Buchko
MCANDREWS, HELD & MALLOY, LTD.
500 West Madison Street, 34th Floor
Chicago, Illinois 60661
(312) 775-8000

Frederick L. Cottrell III (#2555)
cottrell@RLF.com
Anne Shea Gaza (#4093)
gaza@RLF.com
RICHARDS, LAYTON & FINGER
One Rodney Square
920 N. King Street
Wilmington, Delaware 19899
(302) 651-7700

ATTORNEYS FOR PLAINTIFFS ABBOTT LABORATORIES and ABBOTT CARDIOVASCULAR SYSTEMS, INC.

Date: June 12, 2007